American Journal of Diseases of Children

VOLUME 59 MARCH 1940 NUMBER 3

COPYRIGHT, 1940, BY THE AMERICAN MEDICAL ASSOCIATION

LIFE HISTORIES OF NINETY-FIVE CHILDREN WITH CHRONIC ULCERATIVE COLITIS

A STATISTICAL STUDY BASED ON COMPARISON WITH A WHOLE GROUP OF EIGHT HUNDRED AND SEVENTY-ONE PATIENTS

RAYMOND J. JACKMAN, M.D.

J. ARNOLD BARGEN, M.D.

AND

HENRY F. HELMHOLZ, M.D.

ROCHESTER, MINN.

Frequently it has been stated that the nature of chronic ulcerative colitis (thromboulcerative colitis) as it occurs during infancy and childhood, although the disease is basically the same as it is in later life, is prone to be more severe, that the outcome is more likely to be fatal and that a less satisfactory response of the patient to treatment occurs.[1] It has been demonstrated that the opposite is true when this disease afflicts elderly persons or when persons experience symptoms of the disease late in life.

In 1919 Logan [2] reported a series of 117 cases of chronic ulcerative colitis, and in 1923 one of us (Helmholz [3]) made the first report in the literature on the disease as it affects children. This report dealt with 5 cases. In 1924 Bargen's [4] work helped to establish the disease as an entity. During the last two decades considerable information has been added to the knowledge of chronic ulcerative colitis, and in addition, a sufficient period of time has elapsed in which patients whose disease started early in life have been observed. The purpose of this study is

From the Section on Proctology, the Division of Medicine and the Section on Pediatrics of the Mayo Clinic.

1. Brust, J. C. M., and Bargen, J. A.: Chronic Ulcerative Colitis Among Elderly Persons, Minnesota Med. **18**:583-585 (Sept.) 1935.

2. Logan, A. H.: Chronic Ulcerative Colitis: A Review of One Hundred and Seventeen Cases, Northwest Med. **18**:1-9 (Jan.) 1919.

3. Helmholz, H. F.: Chronic Ulcerative Colitis in Childhood, Am. J. Dis. Child. **26**:418-430 (Nov.) 1923.

4. Bargen, J. A.: Experimental Studies on the Etiology of Chronic Ulcerative Colitis: Preliminary Report, J. A. M. A. **83**:332-336 (Aug. 2) 1924.

to determine on a statistical basis the difference, if any exists, between the nature and the course of the disease as it affected 95 children less than 16 years of age and as it affected the whole group of 871 patients (children and adults), which included the 95 child patients previously mentioned.

INCIDENCE

In a study of 871 consecutive cases of the disease in which the patients concerned came to the Mayo Clinic between the years 1925 to 1931, inclusive, Bargen, Jackman and Kerr [5] found that 95 patients, or 10.9 per cent, had been afflicted by chronic ulcerative colitis prior to their sixteenth year of life. This factor of age would indicate, then, that about 1 of every 11 patients suffering from chronic ulcerative colitis as encountered at the Mayo Clinic is afflicted by the disease early in life. Of the total number of patients registered at the Mayo Clinic during the aforementioned seven year period, 5.1 per cent consisted of patients who were treated in the Section on Pediatrics. Yet, as noted, 10.9

TABLE 1.—*Ages at Which the Onset of Symptoms Occurred Among Ninety-Five Children*

Age, years.....	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Total
Patients.....	3	2	3	1	3	3	2	5	5	11	11	10	9	11	16	95

per cent of the total group of 871 patients having chronic ulcerative colitis experienced the onset of the disease during infancy or childhood. One of every 274 persons encountered in the Section on Pediatrics had chronic ulcerative colitis, whereas in the group as a whole the condition was found in a proportion of 1 to each 569 patients registered. This would indicate that chronic ulcerative colitis is not as uncommon in childhood as is generally believed.

Sex Incidence.—In our group of 95 patients who were less than 16 years old the disease was more common among the boys (57 patients, or 60 per cent) than among the girls (38 patients, or 40 per cent). In the entire group there were 491 male patients (or 56 per cent) and 380 female patients (or 44 per cent).

Age Incidence.—The number of patients in each year of life according to the onset of the symptoms is listed in table 1. It should be noted that there is a gradual increase in the number of patients who acquired the disease as the ages progress through to the age of 15. Approximately two thirds of the children experienced the onset of the disease after the age of 9. The curve for the age incidence of all the patients

5. Bargen, J. A.; Jackman, R. J., and Kerr, J. G.: Studies on the Life Histories of Patients with Chronic Ulcerative Colitis (Thrombo-Ulcerative Colitis) with Some Suggestions for Treatment, Ann. Int. Med. **12**:339-352 (Sept.) 1938.

suggests that the peak occurs during the late twenties, with a progressive decline as patients approach old age.

Seasonal Incidence.—Among those patients from whom the month of the onset of the disease could be elicited definitely, it was found that the majority of them dated the onset, as well as the relapses, as occurring in those months in which infections of the upper part of the respiratory tract are especially likely to occur.

Geographic Distribution.—Nothing significant could be learned from a study of the geographic distribution of the patients. In general, the geographic distribution was in keeping with the distribution of all the patients coming to the clinic and definitely was not in keeping with the distribution of localized outbreaks of amebic or bacillary dysentery.

TABLE 2.—*Predisposing Factors in Childhood as Reported by the Whole Group of Eight Hundred and Seventy-One Patients*

Predisposing Factors	Number of Cases
Measles*	2
Chickenpox*	1
Scarlet fever*	1
Colds	8
Sore throat	5
Dietary indiscretion	2
Influenza	8
Surgical intervention	2
Trauma to abdomen	1
Pneumonia	1
Infection of scalp, extensive	1

* Only 4 cases of diseases of childhood were noted as possible predisposing factors.

PREDISPOSING FACTORS

A large majority of the children, as well as the adults, were unable to associate the onset of the disease with any definite predisposing factor. The physician might presume that the diseases of childhood would be an important factor in the development of chronic ulcerative colitis. However, in our study only 4 of the whole group of 871 patients dated the onset of their colitis to the occurrence of either an infectious disease or a disease of childhood (table 2). Nine patients reported that their condition had started during or shortly after an acute infection of the upper part of the respiratory tract, such as tonsillitis or pneumonia. Two patients stated that their condition had started after they had committed a dietary indiscretion, and the disease afflicted 1 patient after the patient had sustained a severe blow to the abdomen. Two patients dated the onset of their condition to a surgical procedure, 1 to an appendectomy and the other to repair of an anorectal fistula.

NATURE OF THE ONSET

In reviewing the histories of these patients, we classified the character of the onset of symptoms into two groups for purposes of comparison. 1. Insidious symptoms: These were reported by those patients whose predominant symptom was the passage of blood with stools and who had from one to five formed or semiformed stools in twenty-four hours; these patients were afebrile and had little or slight evidence of toxemia or debilitation, and their condition had a tendency to slow progression; the feature which usually brought the patients to seek medical advice was the presence of blood in the stool. 2. Severe or fulminating symptoms: These were reported by those persons in whom the onset of the disease was abrupt and accompanied by abdominal cramps, bloody and purulent rectal discharges, fever, toxemia and dehydration, usually of such severity as to require them to go to bed; the patients had a tendency to maintain their status, to improve or to decline rapidly.

TABLE 3.—*Character of the Onset of Symptoms of Ninety-Five Children as Compared with the Character of the Onset of Symptoms of the Whole Group of Eight Hundred and Seventy-One Patients*

Character of the Onset	Children		Group as a Whole	
	Number	Percentage	Number	Percentage
Insidious	22	23	444	50.9
Severe or fulminating	73	77	427	49.1
Total	95	100	871	100.0

As noted in table 3, 73 patients, or 77 per cent of the group of 95 children, were afflicted by chronic ulcerative colitis which had started in the severe or fulminating form, whereas only 427, 49.1 per cent of the whole group of 871 patients, were classified in this column.

COMPLICATIONS

In table 4 are listed the conditions which we have called complications; a comparison is made between these complications as they affected the group of 95 children and as they affected the whole group of 871 patients. In general, there is not a significant variation in these percentages when the two groups are compared on such a basis. However, it is interesting to notice the relatively high incidence of carcinoma of the colon among the group of 95 children (6 patients, or 6.3 per cent) as compared with the whole group (28 patients, or 3.2 per cent).

It may not be entirely clear why the incidence should have been almost twice as much among the 95 children in the former group as it was among the whole group (871 patients), particularly when the

older ages, that is, the sixth and seventh decades, are usually considered the time of life when malignancy is most likely to develop, but it would seem reasonable to suggest again that neoplastic change in the large intestine at least not infrequently results from disorderly and uncontrolled repair of tissue.[5a] It is generally believed that one phase in the development of carcinoma of the colon is the stage of polyposis or adenomatosis; yet the incidence of polyposis was slightly higher for the total group (16.2 per cent) than it was for the 95 children (14.7 per cent).

TABLE 4.—*Distribution of the Complications and Sequelae* * *Among Forty-Five of the Ninety-Five Children as Compared with the Complications and Sequelae Among Three Hundred and Sixty of the Whole Group of Eight Hundred and Seventy-One Patients*

Complication	Children		Group as a Whole	
	Cases, Number	Percentage	Cases, Number	Percentage
Polyposis	14	14.7	141	16.2
Stricture	14	14.7	98	11.2
Anal abscess and fistula	5	5.3	73	8.3
Arthritis	6	6.3	55	6.3
Erythema nodosum	1	1.0	9	1.0
Pyoderma gangraenosum	0	0.0	4	0.4
Perforation	2	2.0	10	1.1
Hepatic abscess	0	0.0	4	0.5
Carcinoma of colon †	6	6.3	28	3.2
Phlebitis	1	1.0	2	0.2
Iritis	0	0.0	5	0.5
Deafness	0	0.0	5	0.5
Splenomegaly	2	2.0	0	0.0
Nephritis	1	1.0	12	1.4
Psychoses	0	0.0	9	1.0
Massive hemorrhage	1	1.0	4	0.5
Endocarditis	1	1.0	9	1.0
Renal calculus	0	0.0	8	0.9
Pyelitis	1	1.0	0	0.0
Multiple complications	9	9.5	132	15.2
Total individuals with complications	45	47.4	360	41.3

* As of March 1, 1938.

† In general, the only significant difference in complications between the two groups is the relatively high incidence of carcinoma of the colon among children (6.3 per cent).

The mechanism by which a polyp becomes entirely transformed into cells which assume independent growth is unknown. Likewise, the length of time required by a polyp to do this is unknown. It is definitely known, however, that some polyps of the colon do become malignant. Kennedy and Weber [6] have emphasized the malignant propensities of adenomatous polyps that afflict children, whether they occur singly or as part of a diffusé process in the colon or rectum.

5a. Bargen, J. A.: Causes of Colonic Cancer: Clinical Support of Current Hypotheses, South. M. J. **32**:627-632 (June) 1939.

6. Kennedy, R. L. J., and Weber, H. M.: Polyposis of the Colon in Children, Am. J. Dis. Child. **42**:69-76 (July) 1931.

The high incidence of carcinoma in both groups might be significant in view of the fact that the incidence of carcinoma of the intestine as a factor in mortality for 1923 to 1929 inclusive, according to the United States Department of Commerce, was 0.011 per cent. The incidence of carcinoma of the large intestine among patients at the Mayo Clinic during these years was 0.86 per cent. These observations would point to one direction that the search for the cure of carcinoma might take.

The percentage of total complications was a little higher for the 95 children (47.4 per cent) than it was for the whole group (41.3 per cent), but multiple complications were considerably greater for the whole group (15.2 per cent) than for the 95 children (9.5 per cent). Several complications occurred among the adults which did not occur among the children, such as renal calculus, psychoses, deafness, iritis,

TABLE 5.—*Mortality* Among Ninety-Five Medically and Surgically Treated Children as Compared with the Mortality* Among Eight Hundred and Seventy-One Medically and Surgically Treated Patients of the Whole Group*

Cause of Death	Children		Group as a Whole	
	Patients, Number	Percentage	Patients, Number	Percentage
Patients having thromboulcerative colitis on whom a surgical attempt was made to relieve condition	9	9.5	67	7.7
Progressing thromboulcerative colitis (no surgical treatment)	7	7.4	44	5.05
Carcinoma of rectum	2	2.1	2	0.02
Nephritis	1	1.1	4	0.04
Pneumonia	0	0.0	4	0.04
Hemorrhage	0	0.0	3	0.03
Pulmonary abscess	0	0.0	1	0.01
Hepatic abscess	0	0.0	2	0.02
Perforation of colon	0	0.0	6	0.07
Exophthalmic goiter	0	0.0	1	0.01
Anal abscess	3	3.1	1	0.01
Death unrelated to colonic disease	0	0.0	13	1.5
Total deaths among patients treated medically and surgically	22	23.2	148	17.0

* As of March 1, 1938.

hepatic abscess and pyoderma gangraenosum. The last-named conditions have been encountered among children not included in this group.

ANALYSIS OF DEATHS

All the deaths which occurred in a period of fourteen years were considered among the group of 871 patients (table 5). One hundred and forty-eight, or 17 per cent, had died before March 1, 1938. Of these, 13 patients died from causes unrelated to their intestinal disease. Among the group of 95 children, 22 patients, or 23.2 per cent, had died before March 1, 1938. All the deaths in the last-mentioned group were

caused directly or indirectly by their intestinal disease. The average duration of life from the onset of the disease to death was nine years. The shortest period during which any single patient had symptoms of chronic ulcerative colitis was three months; the longest was twenty years. The causes of death among these 22 patients of the group of 95 children, as well as among 148 patients of the whole group, are listed in table 5.

Among the 95 children, 20 underwent some form of abdominal surgical intervention for relief of the colitis, its complications or for other unrelated abdominal pathologic conditions. Twelve of the 20 patients were operated on at the Mayo Clinic and 8 were operated on elsewhere. The type and result of the operative procedures performed are listed in table 6. It will be noted that 8 of the 12 patients for whom ileostomies were performed died as a result of the procedure. The condition of 2 was made worse and that of 2 was improved.

TABLE 6.—*Type of Surgical Intervention and End Results, Twenty of Ninety-Five Children Operated On**

Surgical Procedure	Patients Operated On			
	Patients	Died Post-operatively	Symptoms Aggravated	Patients Improved
Ileostomy	12	8	2	2
Appendicostomy, cecostomy	3	..	1	2
Appendectomy	3	..	..	..
Ileocolostomy, resection of right portion of colon	1	..	1	..
Surgical exploration	1	1	..	..
Total	20	9	4	4

* Twelve of the 20 patients were operated on at the Mayo Clinic; 8 were operated on elsewhere.

Among the group of 871 patients, 175 persons underwent 192 operations, 87 of which were performed at the Mayo Clinic and 105 elsewhere. Among the group of 95 children, 20 underwent surgical procedures, 12 of which were done at the clinic and 8 elsewhere (table 6). Seventeen of 20 surgical procedures were performed on these children to relieve symptoms or conditions directly related to colitis: 12 ileostomies, 3 cecostomies, 1 resection of the right portion of the colon and 1 surgical exploration. Nine, or more than half, of the 17 patients died as a result of the surgical intervention; 4 children were made worse by the procedure, and 4 were improved.

STATUS OF PATIENTS AT LAST OBSERVATION

A comparison of the two groups as to the condition of the patients at our last observation was difficult, principally because the nature of the disease tends toward chronicity and is frequently characterized by

remissions and exacerbations. For purposes of comparison, however, we have classified (table 7) the condition of the patients when last observed as:

1. Free of symptoms. Under this heading are grouped those persons who had been free of all symptoms referable to the colon or complications thereof for a period of two or more years. Objective evidence of the disease, such as deformity of the colon, may have remained, but there was no subjective evidence of the disease. Eleven and six-tenths per cent of the children were included in this group, whereas 19.9 per cent of the other group were considered to be symptom free. Five of the 11 symptom-free children had neither objective nor subjective evidence of any remaining disease.

2. Having active disease. Under this heading are listed those persons whose status varied from complete invalidism to mild episodes of the disease. Also in this category are included those persons who, although

TABLE 7.—*End Results* of the Treatment of Eight Hundred and Seventy-One Patients Compared with the End Results of the Treatment of Ninety-Five Children Who Were Observed for from Seven to Fourteen Years*

Result	Children		Group as a Whole	
	Patients	Percentage	Patients	Percentage
Free of symptoms	11	11.6	173	19.9
Having active disease †	62	65.3	550	63.2
Deceased	22	23.2	148	17.0
Total	95	100.0	871	100.0

* As of March 1, 1938.

† The status of the active disease was grouped into satisfactory and unsatisfactory progress. Two hundred and ninety-seven (34 per cent) of the group taken as a whole and 32 (33.7 per cent) of the children were making satisfactory progress, whereas 253 (29 per cent) of the group taken as a whole and 30 (31.6 per cent) of the children were making unsatisfactory progress.

they may not have had any activity of their disease, still had symptoms, because of shortening, narrowing or other disordered physiologic aspects of the colon. Sixty-five and three-tenths per cent of the children, as compared with 63.2 per cent of the adult group, were included in this classification.

Twenty-three and two-tenths per cent of the children were dead, as contrasted with 17.0 per cent of the adult group, at the end of our period of consideration (March 1, 1938).

SUMMARY

A comparative study on a statistical basis has been made between a group of 95 children suffering from chronic ulcerative colitis and the whole group of 871 patients, including both children and adults.

Chronic ulcerative colitis is not as rare during infancy and childhood, that is, prior to the sixteenth year of life, as is generally believed. In a study of a group of 871 patients, it was found that 95 of them (or 10.9 per cent) were afflicted with chronic ulcerative colitis in childhood. In the seven year period of consideration (1925 to 1931 inclusive), 1 of every 274 patients encountered in the Section on Pediatrics of the Mayo Clinic had chronic ulcerative colitis, whereas in the group as a whole the condition was found in the proportion of 1 to 569 of the patients registered.

As to the predisposing factors and the factors affecting relapses of the disease, there is comparatively little difference between the group of children and the group as a whole. Among adult patients infections of the upper portion of the respiratory tract and sore throat were the most pertinent predisposing factors. Only 4 of the entire group studied indicated that acute infectious fevers of childhood had been a factor in the onset of chronic ulcerative colitis. Two patients experienced symptoms after being afflicted with measles, 1 after having had chickenpox and 1 after an attack of scarlet fever.

The onset of the disease can be said to be insidious, severe or fulminating. As compared with the adult group, more children have severe or fulminating symptoms at the onset of the disease.

Chronic ulcerative colitis is, in general, a chronic disease for which the percentages both of patients cured and of those patients free of symptoms are comparatively small. Because of its chronicity it would seem probable that the frequency of complications (for instance, polyposis and stricture) would be in direct proportion to the number of years that the patient has had the disease; our study would indicate this prediction to be true. Forty-five of the group of 95 children, or 47.4 per cent, had complicating factors. This is a somewhat higher percentage than that for the entire group of 871 patients.

The incidence of carcinoma of the large intestine was 3.2 per cent for the entire group of 871 patients. Carcinoma occurred as a complication in 6.3 per cent of our group of 95 patients in whom the onset of the colitis occurred before the sixteenth year of life.

Although the disease is particularly devastating when it occurs during childhood, this does not preclude the living of a normal span of life by a child so afflicted, and our study would indicate that when a patient has survived the first years of the onslaught of the disease, the tendency in general is that the disease becomes milder or, perhaps, the patient becomes progressively better able to tolerate the condition.

DISSEMINATED GIANT CELL REACTION

A POSSIBLE PRODROME OF MEASLES

WALTER A. STRYKER

CHICAGO

The significance of the occurrence of giant cells in association with pneumonia in children has received attention from numerous investigators without any definite conclusions or agreement being attained. The most recent complete review of the subject was made by Moore and Gross [1] in 1930. The authors distinguished four types of giant cells, which will be discussed later, and made the statement that "giant cells in association with pneumonia have no specific cause."

Recently a case has come under my observation in which pneumonia was proved histologically to be associated with a widespread formation of giant cells. A presentation of this case is made because in type and location the cells differed from any described by Moore and Gross and because the case may represent a generalized reaction in the prodromal stage of measles.

REPORT OF A CASE

History.—A girl aged 27 months was admitted to the Bobs Roberts Memorial Hospital for Children (service of Dr. Bengt Hamilton) for emergency treatment on the evening of March 12, 1938. The history was given by the mother. About three weeks prior to admission, the child, who was staying at a nursery school, had shown evidence of a slight cold and fever. She was not too ill, however, to remain in the nursery school. When she was visited a week later, the cold and fever were as before. One week before admission the cold appeared worse, there was a slight cough and the child was fretful. Three days before admission she was restless and dyspneic, with slight cyanosis. Since the child was under the care of the nursery, the history of medication was not known. Except for German measles when she was 15 months old, her past history was not important.

Examination and Course.—Physical examination revealed dyspnea and palpable cervical glands. Examination of the chest showed bilaterally decreased excursion, increased tactile fremitus, dulness over the cardiac area and the upper posterior area on the right side and numerous mucous rales over the entire chest. The temperature was 104.8 F. The clinical impression was of bronchopneumonia. The child was placed in an oxygen tent, but the fever increased, the dyspnea

---

Presented before the Chicago Pathological Society, May 8, 1939.

From the Department of Pathology, The School of Medicine of the Division of Biological Sciences, University of Chicago.

1. Moore, R. A., and Gross, P.: Giant Cells in Inflammations of the Lung in Children, Am. J. Dis. Child. **40**:247 (Aug.) 1930.

remained marked and the pulse became weaker. A clysis of 5 per cent dextrose was not completed, and the child died three and one-half hours after admission. No laboratory work was done.

Postmortem Examination.—An autopsy was performed eleven hours after death. The child appeared well nourished and externally showed only pallor of the skin. The right pleural cavity contained approximately 20 cc. of an amber fluid; the left pleural cavity was normal. The trachea contained a small amount of frothy mucus; its mucosa was markedly hyperemic. Both lungs were increased in weight: the left weighed 145 Gm., and the right 170 Gm.[2] The pleural surfaces were smooth. All the lobes of both lungs were consolidated except the upper portion of the upper lobe of the right lung, in which nodules could be palpated. On section the lungs were seen to be dark red, firm and moist, but only in the lower lobe of the right lung was the tissue friable. The bronchi appeared abnormally thick walled and contained mucus. Lymphatic tissue was prominent throughout both lungs. The peribronchial lymph nodes were enlarged, those about the right bronchus forming a mass 3 by 1.5 by 1 cm., and they appeared moist on section. The liver, kidneys and myocardium showed fatty change, and all the viscera were pale.

The histologic changes were more spectacular. The tissues were fixed in Zenker's solution and were embedded in pyroxylin. The sections were stained with hematoxylin and eosin, Mallory's connective tissue stain, Maximow's eosin-azur stain, Cooper's stain for acid-fast organisms, iron-hematoxylin stain, carbol-thionine and the Gram-Weigert stain. Several sections of lung, taken from various lobes, showed similar pictures. There was acute necrotizing bronchitis; the lumens were filled with an exudate consisting chiefly of polymorphonuclear leukocytes. The bronchial mucosa was in some places partially destroyed and in others entirely absent. In some bronchi there was metaplasia of the columnar epithelium to a stratified squamous type. The bronchial walls were thickened by connective tissue containing many round cells. Surrounding the bronchi were areas of bronchopneumonia, patchy in distribution. The alveoli were filled with polymorphonuclear leukocytes and contained occasionally many red blood cells. Some alveoli contained only protein precipitate. Only an occasional cell of the septal macrophage type was seen, and there was little free fibrin. There also was interstitial pneumonitis, especially in the areas adjacent to the bronchi; evaluation of this was difficult because of the exudate into the alveoli. The most striking feature, however, was the large number of giant cells (fig. 1). These were of four distinct types. Some of the cells lying free in the alveoli were large and had forty or more nuclei, which appeared to be separate rather than lobed; the cytoplasm was eosinophilic and slightly granular and did not contain vacuoles or pigment. A second type of giant cell in the alveoli showed a single-lobed nucleus, and in the cytoplasm vacuoles could be seen. Other giant cells were present in the bronchi, some lying free in the lumens with the polymorphonuclear exudate or, where there had been a loss of bronchial mucosa, lying against the wall. Some of them appeared to be the product of desquamented but fused epithelium. More spectacular was the presence in the bronchial walls, beneath the basement membrane, of numerous giant cells similar to those seen in the alveoli, with separate nuclei and no vacuoles in the cytoplasm (fig. 2). In the alveolar walls giant cells of the megakaryocyte type were seen lying in the capillaries, shaped by the capillary walls.

---

2. The average normal weight for the lungs of a 27 month old child are left 76 Gm. and right 88 Gm. (Coppoletta, J. M., and Wolbach, S. B.: Body Lengths and Organ Weights of Infants and Children, Am. J. Path. **9**:55, 1933).

Throughout the involved portions of the lung, but more prominent immediately adjacent to the bronchi, there was an increase in fibrous tissue. This was brought out well by the Mallory stain. There was also some edema of the septums, causing a separation of preexisting connective tissue fibers and hence giving an appearance of greater increase in fibrous tissue.

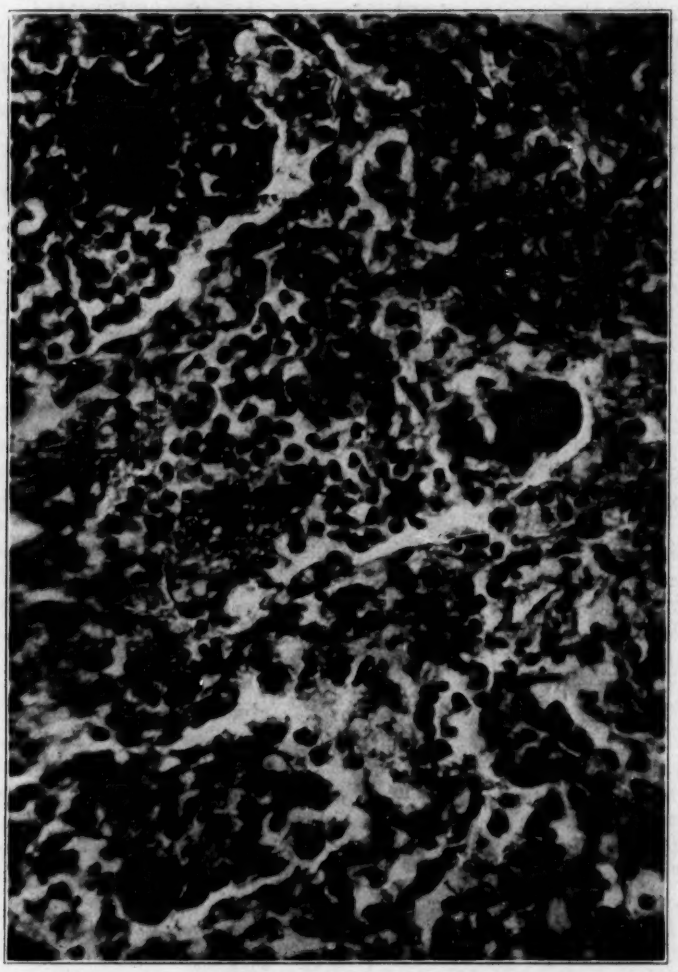

Fig. 1.—The lung, with various types of giant cells (× 323).

A section through the hilum of the lung showed a large bronchus the wall of which was infiltrated with many polymorphonuclears, round cells and giant cells. In the surrounding mucous glands there were many giant cells similar in size and appearance to the first group described in the lung; of these some lay free in the lumens and some among the cells of the glands, and many were present in the interstitial connective tissue. Some of the cells appeared to be related to the endothelium of the blood vessels. Cells of acute and chronic inflammation were also

present in the interstitial tissues. The trachea showed changes similar to those of the large bronchus; in the mucous glands were numerous giant cells.

The tracheobronchial lymph nodes revealed hyperplasia of both the reticular cells and the lymphocytes. Polymorphonuclears were present in the sinuses, especially in the peripheral sinuses. Throughout the nodes were many giant

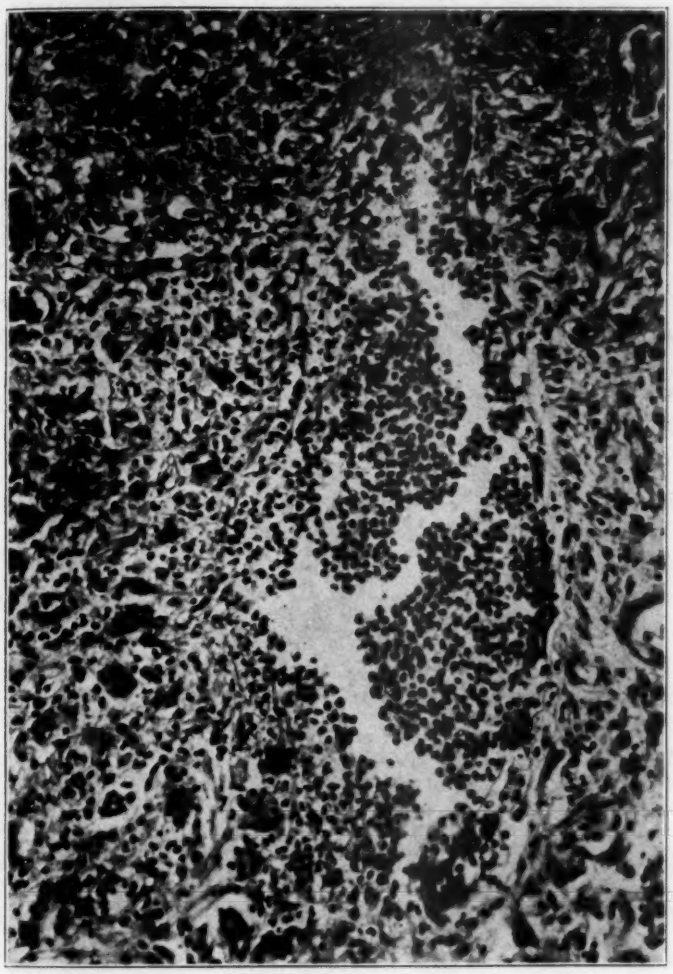

Fig. 2.—A bronchus, with polymorphonuclear leukocyte exudate in the lumen (× 177). The giant cell in the lumen is a pseudo giant cell; the giant cells beneath the basement membrane are of the specific type.

cells morphologically like those in the lungs and mucous glands (fig. 3). These were present in both the sinuses and the medullary cords. Lying in the connective tissue surrounding the nodes were other giant cells, with no apparent relation to the blood vessels. The lymphatic vessels surrounding the nodes were distended with protein precipitate in which were mixed a few leukocytes.

In the spleen, many of the lymphoid follicles contained reaction centers, and others showed hyaline change or hemorrhage. The pulp was packed with red blood cells, and among these were numerous giant cells. These were of two types, some resembling megakaryocytes, with a budding type of nucleus, and others resembling the giant cells seen in the lung, with separate nuclei. They were not

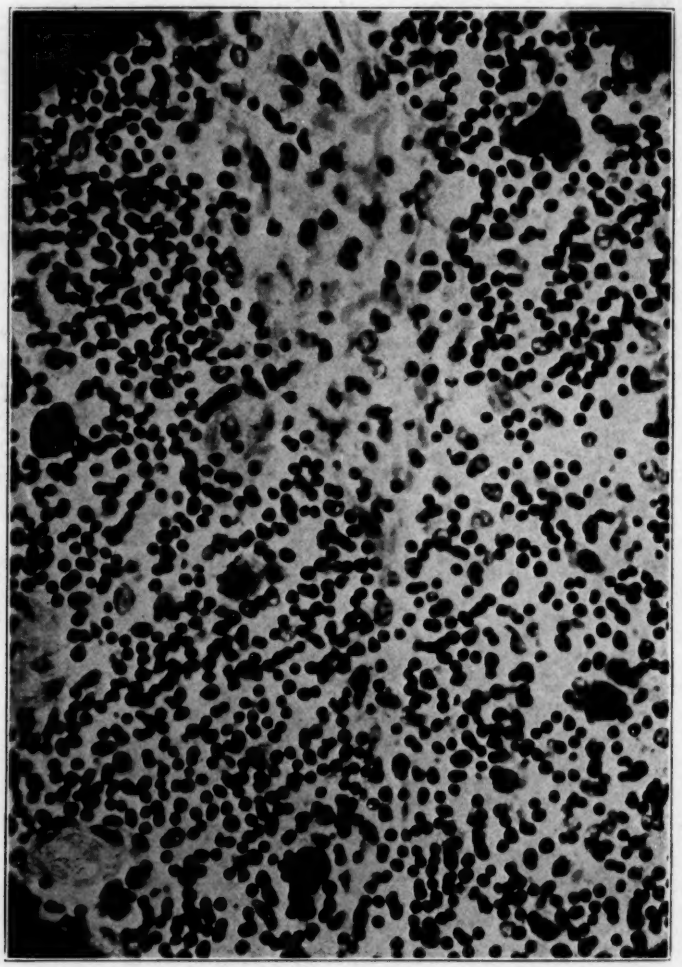

Fig. 3.—Specific giant cells in the medullary cords of a tracheobronchial lymph node (× 357.7).

as large as those in the lung and adjacent structures. A Peyer patch in the ileum showed similar hyperplasia, with marked reaction centers; in the center of one of these there was a cell with multiple nuclei, not as large as the other giant cells. In the thymus no giant cells were seen. Likewise none were seen in the bone marrow, where megakaryocytes were normal in number. A section of a blood clot from the heart contained many polymorphonuclears but no giant cells or

megakaryocytes. The myocardium, liver and kidneys showed the fatty change; the pancreas, thyroid, colon, adrenals and ovaries were essentially normal.

The Maximow stain showed the giant cells in the lungs, mucous glands and peribronchial lymph nodes to have an eosinophilic cytoplasm, slightly granular; the nuclei were vesicular, with a rim of chromatin and small flecks of chromatin within. In some (degenerating?) the cytoplasm was more basophilic and the nuclei were hyperchromatic, with evenly distributed chromatin. The megakaryocytes in the bone marrow revealed eosinophilic cytoplasm and nuclei in which the chromatin was evenly distributed. In the spleen many of the large cells were similar to the megakaryocytes of the bone marrow; others were like the degenerating forms of the giant cells in the lung. Iron-hematoxylin stain added no further information.

No cultures of the postmortem material were made. The carbolthionin and the Gram-Weigert stain revealed numerous gram-positive cocci in the lungs and tracheobronchial lymph nodes, but none of these were definitely present in the giant cells. The Cooper stain gave uniformly negative results.

Summary.—Giant cells were found in the pulmonary alveoli, in the bronchi, in the sinuses and medullary cords of the lymph nodes, in the lumens and walls of the mucous glands, in the interstitial connective tissue surrounding the lymph nodes and between the mucous glands, in the spleen and in the lymphatic tissue of the ileum. The giant cells in the lungs probably represented four different types: fused epithelium, cells phagocytic of fats, megakaryocytes and a fourth type, to be discussed later. Those in the spleen were megakaryocytes plus the fourth type, and those in the lymph nodes were believed to be all of this specific type.

COMMENT

A study of the literature and of their 5 cases led Moore and Gross [1] to conclude that four types of giant cells would be found in the lungs in various kinds of pneumonic processes. (In their discussion, as in this, the specific giant cells of tuberculosis and other granulomatous diseases were excluded.) Two of their four types were in reality pseudo giant cells: one the result of fusion of hyalinized exudate and the other representing a fusion of desquamated bronchial epithelium. The third type was a phagocytic cell, described as often containing vacuoles or pigment or occurring in desquamative processes without other inflammation. These may have represented the foreign body giant cell often seen in cases of lipoid pneumonia or with other foreign bodies. The fourth type of giant cell was called the typical Langhans cell and had acidophilic cytoplasm and nuclei arranged peripherally. The authors included in this type many of the giant cells of previous reports. A study of the original articles would lead one to include the cells of this type with the pseudo giant cell previously mentioned, formed by fusion of desquamated epithelium. In either case, the fact of primary importance in this discussion is that the location of the giant cells of all four types was only in the alveolar or the infundibular spaces. Cells similar in structure to the phagocytic type were seen occasionally in the alveolar walls, but the use of elastic tissue stains by other investigators in similar

cases has indicated that such cells usually lie outside the elastic fibers, and Moore and Gross expressed the opinion that the cells in their cases were of alveolar epithelial origin.

The first account of giant cells associated with pneumonia, usually in children, was by Buhl [3] in 1872. The subject has been of interest chiefly to Continental investigators, and most of the reports are by them.[4] In all but two of these reports the cells were stated to be present only in the alveoli or the bronchi. Masson and Paré [4] observed them in the lumens of bronchial glands. In one case reported by Chown,[4] a large paratracheal lymph node of a syphilitic child was said to contain a few giant cells; no further description of the cells was given. They tend to occur more frequently after certain infections in which there is marked desquamation of epithelium (measles, whooping cough, influenza and diphtheria) or after subacute pneumonia. The best theory as to their origin is that of fusion or incomplete division of desquamated bronchial and alveolar epithelium. In Chown's [4] recent paper he suggested a relation between the metaplasia of vitamin A deficiency and the appearance of giant cells; however, he reached no conclusions and admitted that in none of the numerous previously reported cases of death from the vitamin deficiency had the presence of giant cells been demonstrated. In general, the giant cells seen in the case here presented were more disseminated and were structurally different.

In 1931 Warthin [5] reported 4 cases in which there were numerous large giant cells in the tonsils and pharyngeal mucosa in the prodromal stage of measles. The appearance and location of the cells were suf-

3. Buhl, L., cited by Karsner, H. T., and Meyers, A. E.: "Giant-Cell Pneumonia," Arch. Int. Med. **11**:534 (May) 1913.

4. Aufrecht, E., cited by Moore and Gross.[1] Chown, B.: Giant Cell Pneumonia of Infancy as a Manifestation of Vitamin A Deficiency, Am. J. Dis. Child. **57**: 489 (March) 1939. Durch, H.: Studien über die Aetiologie und Histologie der Pneumonie im Kindesalter und der Pneumonie im Allgemeinen, Deutsches Arch. f. klin. Med. **58**:368, 1896. Feyrter, F.: Ueber die Masernpneumonie, Virchows Arch. f. path. Anat. **255**:753, 1925. Friedlander, C.: Experimentelle Untersuchungen über chronische Pneumonie und Lungenschwindsucht, ibid. **68**:325, 1876. Hecht, V.: Die Riesenzellenpneumonie im Kindesalter, Beitr. z. path. Anat. u. z. allg. Path. **48**:263, 1910. Karsner, H. T., and Meyers, A. E.: "Giant-Cell Pneumonia," Arch. Int. Med. **11**:534 (May) 1913. Kromayer, E.: Ueber die sogenannte Katarrhal-Pneumonie nach Masern und Keuchhusten, Virchows Arch. f. path. Anat. **117**:452, 1889. Martin, J. F.; Girard, P., and Vincent, A.: Contribution à l'étude anatomique des broncho-pneumonies à plasmodes, J. de méd. de Lyon **13**:771, 1932. Masson, P., and Paré, L.: Un cas de broncho-pneumonie à plasmodes, Ann. d'anat. path. **8**:13, 1931. Steinhaus, F.: Histologische Untersuchungen über die Masernpneumonie, Beitr. z. path. Anat. u. z. allg. Path. **29**:524, 1901.

5. Warthin, A. S.: Occurrence of Numerous Large Giant Cells in the Tonsils and Pharyngeal Mucosa in the Prodromal Stage of Measles: Report of Four Cases, Arch. Path. **11**:864 (June) 1931.

ficiently characteristic so that after his first case he was able to make the prediction of measles without knowledge of the patient's postoperative clinical history. Subsequently, similar cells were observed in the tonsils in the prodromal stage of measles by Finkledey.[6] In 1932 Herzberg [7] reported the finding of the cells in a surgically removed appendix and the appearance of the measles rash four days after the operation. Davidsohn and Mora [8] in 1932 reported 2 cases in which the characteristic cells were found in the appendix, with postoperative development of measles. Similar reports have since been made by Finkledey,[9] Fischer,[10] Schultze,[11] Ravina and Lévy-Lang,[12] Wegelin,[13] Bullowa, McCabe and Wishik [14] and Semsroth.[15] The giant cells in all cases were similar in appearance: The cytoplasm was usually abundant and might be basophilic or eosinophilic; from three to fifty round nuclei were present, and a characteristic feature was the grouping of the nuclei in the center of the cell. The cells varied in location; in some cases they were only in the follicles and in others in various parts of the lymphatic tissue, or they were seen migrating into the mucosa. In one of Wegelin's [13] 3 cases, the mesenteric lymph nodes also contained the cells. In 1935 Hathaway [16] reported on a child who died of a ruptured appendix; a sibling of the patient was ill with measles, but there was no rash on the patient. Histologic examination showed giant cells in the peribronchial, retroperitoneal and peripancreatic lymph nodes and in the spleen.

6. Finkledey, W.: Ueber Riesenzellbefunde in den Gaumenmandeln, zugleich ein Beitrag zur Histopathologie der Mandelveränderungen in Maserninkubationsstadium, Virchows Arch. f. path. Anat. **281**:323, 1931.

7. Herzberg, M.: Giant Cells in the Lymphoid Tissue of the Appendix in the Prodromal Stage of Measles: Report of an Isolated Case, J. A. M. A. **98**:139 (Jan. 9) 1932.

8. Davidsohn, I., and Mora, J. M.: Appendicitis in Measles, Arch. Path. **14**: 757 (Dec.) 1932.

9. Finkledey, W.: Riesenzellbefunde bei akuter Wurmfortsatzentzündung, Virchows Arch. f. path. Anat. **284**:518, 1932.

10. Fischer, W.: Ueber die Diagnose der Masern im Prodromalstadium, Beitr. z. path. Anat. u. z. allg. Path. **91**:474, 1933.

11. Schultze, W. H.: Der Wurmfortsatz im Prodromalstadium der Masern, München. med. Wchnschr. **80**:576, 1933.

12. Ravina, A., and Lévy-Lang, P.: Le diagnostic histologique de la rougeole, Presse méd. **45**:821, 1937.

13. Wegelin, C.: Zur histologischen Diagnose der Masern, Schweiz. med. Wchnschr. **67**:1, 1937.

14. Bullowa, J. G. M.; McCabe, E. J., and Wishik, S. M.: Acute Appendicitis in the Exanthems, Am. J. Dis. Child. **53**:1029 (April) 1937.

15. Semsroth, K. H.: Paper read before the American Association of Pathologists and Bacteriologists, 1939; personal communication to the author.

16. Hathaway, B. M.: Generalized Dissemination of Giant Cells in Lymphoid Tissue in the Prodromal Stage of Measles, Arch. Path. **19**:819 (June) 1935.

Examination of the lymphoid tissue of the gastrointestinal tract, including the appendix, and the mesenteric lymph nodes failed to reveal the cells. This variability of location was also noted by Warthin.[5] In 1 of the cases he reported, a cervical lymph node failed to contain the cells. Hathaway did not mention tissues other than lymphoid structures.

After the rash of measles has appeared, the giant cells apparently disappear. In a case reported by Davidsohn and Mora,[8] in an appendix removed two days after the appearance of the rash only scarce cells which appeared to be degenerating were seen. In another case, in an appendix removed nine days after the appearance of the rash no giant cells were seen. Alagna[17] in 1908 studied the cells, which appear likewise to be degenerating forms, in the tonsils of patients with measles. Ciaccio[18] two years later reported on the pathologic changes in the viscera in Alagna's cases and found only megakaryocyte-like cells in the capillaries in the lungs. Denton[19] in 1925 and Degen[20] in 1937 reported on the pathologic process of fatal measles; neither author mentioned this type of giant cell, although Denton did describe giant cells of the fused epithelium type lying free in the alveoli. Of 19 patients with postmeasles pneumonia examined post mortem by MacCallum,[21] only 1 showed the fused epithelium type, and no other giant cells were described. Humphreys[22] observed peculiar structures in the pulmonary alveoli of a child who died five days after the appearance of a measles rash. There were large clumped masses of chromatophilic material with little cytoplasm, and they looked like degenerating multinucleate cells. There were also slight peribronchitis and hyperplasia of the basal epithelial layer of many of the bronchi. No giant cells were seen in other organs.

Histologically the giant cells encountered in the case that has been presented were similar to those apparently specific for measles. Sections of the tonsils or of the appendix were not available, but in view of Hathaway's findings this might not be important. With the possibility of the child's having been in the prodromal stage of measles, inquiries were made at the nursery as to any children with measles there at the

17. Alagna, G.: Histopathologische Veränderungen der Tonsille und der Schleimhaut der ersten Luftwege bei Masern, Arch. f. Laryng. u. Rhin. **25**:527, 1911.

18. Ciaccio, C.: Beitrag zur pathologischen Anatomie und zur Mikrobiologie der Masern, Virchows Arch. f. path. Anat. **199**:378, 1910.

19. Denton, J.: Pathology of Fatal Measles, Am. J. M. Sc. **169**:531, 1925.

20. Degen, J. A., Jr.: Visceral Pathology in Measles, Am. J. M. Sc. **194**:104, 1937.

21. MacCallum, W. G.: The Pathology of Pneumonia in the United States Army Camps During the Winter of 1917-1918, Monograph 10, Rockefeller Institute for Medical Research, 1919.

22. Humphreys, E. M.: Personal communication to the author.

time. The school kept no records, and the authorities were not cooperative, but they did admit that there was a child with measles in the nursery during the spring of 1938. The home was adjacent to a large university settlement house, where records of attendance at the settlement nursery were kept, and it was found that during the first two weeks of March 1938 5 of 15 children in the nursery were absent because of measles. These coincidences, while not conclusive, are interesting in view of the histologic data in the case.

In 1938 Broadhurst and associates [23] described the presence of inclusion bodies in the ciliated and columnar cells and in the globoid basal cells of the nasal mucosa and in the cells of the Koplik spots in the buccal cavity. These bodies are demonstrated by staining swabbed material with nigrosin and can sometimes be seen as early as the first day of the disease, even before the appearance of the rash; however, the quantity increases as the disease progresses. Sections were studied in the case here reported by Dr. Broadhurst. No definite conclusion could be reached from the use of fixed tissues, although suggestive inclusions were seen in some cells.[24] Similar staining of an appendix rich in giant cells in a proved case of appendicitis during the prodromal stage of measles gave similar results. (This case is mentioned with the permission of Drs. Otto Saphir and Marion Corrigan of Michael Reese Hospital.) In the material recently reported by Semsroth,[15] inclusion bodies were found in sections stained with hematoxylin and eosin. I have been unable to find these in my material or in the giant cells of the case of Drs. Saphir and Corrigan. Warthin [5] expressed the opinion that the giant cells are defensive and the hope that he would find a clue to the etiologic agent in them. However, more than fifty special staining methods for the demonstration of micro-organisms were unsuccessful.

SUMMARY

A pathologic change in a 27 month old child who died of pneumonia was the presence of multinucleate giant cells in the pulmonary alveoli, bronchi, sinuses and medullary cords of the tracheobronchial lymph nodes, lumens and walls of the bronchial mucous glands, interstitial connective tissues about the lymph nodes and mucous glands, spleen and lymphatic tissues of the ileum. These cells appeared morphologically like those described as specific for the prodromal stage of measles. A history of a possible contact with measles was obtained. Attempts to demonstrate inclusion bodies were inconclusive. This case is not presented as a proved example of the appearance of disseminated giant

23. Broadhurst, J.; MacLean, M. E., and Saurino, V.: Inclusion Bodies in Measles, J. Infect. Dis. **61**:201, 1937.

24. Broadhurst, J.: Personal communication to the author.

cells in the prodromal stage of measles; the existence of similar cells in proved cases, however, suggests the possibility here.

NOTE.—Masugi and Minami [25] have recently reported the presence of giant cells in a child who died four days after the appearance of a measles rash. These cells were only in the alveoli of the lungs, the bronchi and other lumens, and none were seen in the lymph nodes, appendix or spleen. The authors' statement that these cells were of the type specific for measles does not seem justified.

---

25. Masugi, M., and Minami, G.: Ueber einen Fall von Masern mit Riesenzellen an Luftwegen, Mund- und Rachenschleimhaut: Ueber die Einschlüsse an Masernriesenzellen, Beitr. z. path. Anat. u. z. allg. Path. **101**:483, 1938.

STUDIES IN IMMUNITY

VI. CORRELATION OF THE REACTION TO THE SCHICK TEST AND THE DIPHTHERIA ANTITOXIN CONTENT OF THE BLOOD SERUM IN CHILDREN WITH SCARLET FEVER

CARL E. DUFFY, M.S.
AND
A. GRAEME MITCHELL, M.D.
CINCINNATI

In a previous study in this series [1] it was concluded that scarlet fever did not affect the reaction to the Schick test; that is, that there was no difference in the cutaneous reactions to diphtheria toxin during the acute febrile and the convalescent stage of this disease. On the basis of the Schick test the work of other investigators [2] has suggested that scarlet fever increases the susceptibility to diphtheria. Only in the study of Kojis and Craig and in our own were comparisons made of the Schick reactions during the acute and the convalescent stage of scarlet fever in the same group of patients.

PLAN OF STUDY

If, as some investigators have claimed, scarlet fever induces an increase in positive Schick reactions, two explanations may be offered: There may be a decrease in circulating diphtheria antitoxin, or there may be an increased sensitivity of the skin to diphtheria toxin. We decided, therefore, to repeat our previous study and to compare the Schick reactions of patients with scarlet fever with their circulating diphtheria antitoxin content.

From the Children's Hospital Research Foundation and from the Department of Pediatrics of the College of Medicine, University of Cincinnati.

1. Eddy, B., and Mitchell, A. G.: Studies in Immunity: III. Effect of Diseases Other Than Diphtheria on the Schick Test, Am. J. Dis. Child. **40**:985-987 (Nov.) 1930.

2. Kolmer, J. A., and Moshage, E. L.: Schick Toxin Reaction for Immunity in Diphtheria, Am. J. Dis. Child. **9**:189-204 (March) 1915; Note on the Occurrence of Pseudoreactions on the Skin, with Special Reference to the Schick Test, J. A. M. A. **65**:144-146 (July 10) 1915. Park, W. H., and Zingher, A.: Diphtheria Immunity, Natural, Active and Passive: Its Determination by Schick Test, Am. J. Pub. Health **6**:431-445 (May) 1916. Zingher, A.: Schick Test in Poliomyelitis, Scarlet Fever, Measles and in Normal Children, Am. J. Dis. Child. **13**: 247-251 (March) 1917. Hull, T. G.: Schick Test and Scarlet Fever, J. Lab. & Clin. Med. **11**:260-261 (Dec.) 1925. Kojis, F. G., and Craig, J. D.: Effect of Scarlet Fever on Immunity to Diphtheria as Determined by the Schick Test, Am. J. Dis. Child. **49**:383-389 (Feb.) 1935.

TECHNIC

Twenty-two children from 2 to 13 years of age who were suffering from scarlet fever and had no diphtheria bacilli in the nose or throat were studied.

Blood was drawn and allowed to clot. The serum was removed after centrifugation and titrated for its diphtheria antitoxin content according to the method of Fraser.[3] All dilutions of toxin, antitoxin and serum were made with the buffer solution of Glenny, Pope and Waddington.[4] All determinations were made on the same day that the blood was drawn. In every case the blood was obtained before the Schick test was performed.

The toxin used was well aged (two and one-half years old) and obtained from Parke, Davis and Company. The antitoxin used for the controls was obtained from the National Institute of Health, Washington, D. C.

Messeloff and Karsh,[5] among others, have suggested that the occurrence of negative reactions to Schick tests in persons with little or no antitoxin in their blood could be attributed to the use of a deteriorated toxin or to a toxin of questionable potency. In the attempt to avoid such a possibility we used two toxins simultaneously. The Schick tests were performed as follows: One toxin was injected intracutaneously into the upper third of the flexor surface of the left forearm. The other toxin used in the determinations of antitoxin was diluted with buffer solution so that 0.1 cc. contained one fiftieth of the minimum lethal dose, or 1 Schick test dose; 0.1 cc. of this solution was injected into the flexor surface of the right forearm. This dilution of toxin when tested on guinea pigs produced a reaction within the limits recommended in the report of the Permanent Commission on Biological Standardization, London, June 23, 1931. Part of this buffered toxin was heated and used as a control on the middle third of the flexor surface of the left forearm. All 22 children gave identical reactions to both toxins.

RESULTS

The amount of antitoxin per cubic centimeter of serum, the day of hospitalization on which the blood was taken and the results of the Schick tests are given in the table.

As shown in the table, 8 or 36 per cent, of 22 children with scarlet fever gave positive reactions and none of the 8 had as much as 0.002 unit of antitoxin per cubic centimeter of blood serum. Fourteen, or 64 per cent, reacted negatively. All except 2 of the 14 had more than 0.002 unit per cubic centimeter of blood serum. One of these 2 had less than 0.002 unit, and 1 had less than 0.01 unit.

Several of the patients had comparatively high diphtheria antitoxin values late in the convalescent stage of scarlet fever, 1 child showing

3. Fraser, D. T.: Technique of Method for Quantitative Determination of Diphtheria Antitoxin by Skin Test in Rabbits, Tr. Roy. Soc. Canada (Sect. V, Biol. Sc.) **25**:175-181 (May) 1931.

4. Glenny, A. T.; Pope, C. G., and Waddington, H.: Stability of Schick Toxin, J. Path. & Bact. **31**:133-134, 1928.

5. Messeloff, C. R., and Karsh, M. J.: Antitoxin Content of the Blood Serum of Children with Negative Reactions to the Schick Test, Am. J. Dis. Child. **44**: 999-1006 (Nov.) 1932.

0.02 to 0.04 unit on the twenty-second day and another showing 0.04 to 0.1 unit on the twenty-first day.

It is significant that for these patients the borderline between negative and positive reactions appears to be about 0.002 unit per cubic centimeter of blood. This is in close agreement with the observations of Parish and Wright,[6] Fraser and Halpern [7] and Brandon and Fraser.[8]

CONCLUSIONS

A study of 22 patients with scarlet fever, 2 to 13 years of age, whose serum diphtheria antitoxin content was compared with their reaction to the Schick test is reported. Eight (36 per cent) of the 22 children

Correlation of Results of Schick Test with the Diphtheria Antitoxin Content of the Blood of Twenty-Two Children with Scarlet Fever

Age of Patient, Years	Hospital Day	Units of Antitoxin Cc. of Serum	Reaction to Schick Test
3	9th	< 0.002	+
5	11th	< 0.002	+
4	3d	< 0.002	+
10	3d	< 0.002	+
5	18th	< 0.002	+
12	15th	< 0.002	+
12	10th	< 0.002	+
10	17th	< 0.002	+
8	8th	< 0.002	−
2	7th	< 0.010*	−
3	12th	0.002-0.004	−
2	12th	0.002-0.004	−
7	14th	0.005-0.01	−
7	4th	0.005-0.01	−
6	4th	0.005-0.01	−
8	10th	0.01-0.02	−
7	8th	0.01-0.02	−
8	22d	0.02-0.04	−
12	21st	0.04-0.1	−
4	13th	0.1-0.2	−
13	6th	0.2-0.4	−
7	9th	> 1	−

* Insufficient serum for determination of lower values.

gave positive reactions to the Schick test. All of these had less than 0.002 unit of diphtheria antitoxin per cubic centimeter of serum. Fourteen (64 per cent) gave negative reactions, and all except 2 had more than 0.002 unit of antitoxin per cubic centimeter of serum.

From these data it would appear that the borderline between negative and positive reactions to the Schick test in patients with scarlet

6. Parish, H. J., and Wright, J.: Schick Test and Active Immunization in Relation to Epidemic Diphtheria, Lancet **1**:600-604 (March 16) 1935.

7. Fraser, D. T., and Halpern, K. C.: Serial Titrations of Diphtheria Antitoxin Following Toxoid, Canad. Pub. Health J. **26**:476-481 (Oct.) 1935.

8. Brandon, K. F., and Fraser, D. T.: Observations on Interpretation of Schick Tests: Comparison of Schick Test Interpretations Using Different Products on the Same Individual Simultaneously, J. Immunol. **31**:387-399 (Nov.) 1936.

fever is in the neighborhood of 0.002 unit of antitoxin per cubic centimeter of serum, which is in close agreement with the values reported by other investigators for normal children. This evidence, therefore, suggests that there is no increased sensitivity of the skin to diphtheria toxin during scarlet fever, since otherwise it would be expected that positive Schick reactions would be obtained at higher levels of serum antitoxin. This study does not answer the question "Is there a decrease in circulating diphtheria antitoxin in the blood of patients with scarlet fever?"

EFFECTS OF NATURAL AND REFINED SUGARS ON ORAL LACTOBACILLI AND CARIES AMONG PRIMITIVE ESKIMOS

DONALD B. WAUGH, D.D.S.
AND
LEUMAN M. WAUGH, D.D.S.
WITH THE TECHNICAL ASSISTANCE OF MARJORIE P. WAUGH
NEW YORK

A field study was made of the Eskimos of the lower Kuskokwim River area, in the southwestern region of Alaska, the home of the most primitive of the American Eskimos. This region was chosen because of the opportunity afforded to observe both primitive and semicivilized natives. Many of the settlements are so isolated that contact with the white man and particularly with his foods has not been sufficient to effect any sign of dental caries. In a few settlements, on the other hand, where traders have brought in "store" foods, the natives show an exceedingly high incidence of caries. In 1935 we (L. W. and D. W.) showed that 85 per cent of the mouths free from caries contained no lactobacilli.[1] In 1936

This work was made possible by grants from the office of Indian Affairs, United States Department of the Interior, through the cooperation of Dr. J. G. Townsend, Director of Health.

This paper is Unit 4, Section XIII, of "Dental Studies of the Eskimos of North America," directed by L. M. Waugh, D.D.S., Consultant Dentist, Office of Indian Affairs, and Dental Director (Reserve) of the United States Public Health Service.

T. J. Pyle, D.D.S., Supervisor of Dentistry for Alaska, was detailed by his office to aid the starting of the work and assisted in the original examinations of the natives and in the selection of subjects for the experiment; Mrs. Anna C. Schwalbe and Reverend F. Drebert, of the Moravian Mission, Bethel, Alaska, permitted the use of the Moravian church at Napakiak as a laboratory and clinical headquarters; Sammy Full Moon, Quinhagak, Alaska, served as native interpreter and assistant; Mr. Matfey Berezkin, native Alaskan priest of the Russian church, aided in soliciting the good will of the primitive Eskimos of his settlement; Philip Jay, D.D.S., University of Michigan, prepared the culture medium; William J. Gies, Ph.D., Professor Emeritus, Department of Biological Chemistry, Columbia University, gave counsel regarding phases of the research.

1. Waugh, L. M., and Waugh, D. B.: Dental Observations Among Eskimo: VI. Bacteriologic Findings in Most Primitive and Populous Native District of Alaska, J. Dent. Research **15**:317 (Sept.) 1936.

Rosebury and L. M. Waugh,[2] in a similar series of experiments, found that 86.4 per cent of the mouths free from caries showed no lactobacilli and that 80.6 per cent of the mouths with caries had lactobacilli. Both these experiments were carried on in the same general region as was the present work.

Observations and data obtained by L. M. Waugh [3] among the Labrador Eskimos indicate that when the natives remain on their primitive diet, which is practically free from fermentable carbohydrates, caries is unknown, but that when "white man's" food is introduced, caries appears and is prevalent in proportion to the amount of "white man's" food indulged in. His observations and studies of native diets among the Eskimos of Arctic Alaska [4] bear out the same findings. He has also furthered these results by field studies among the primitive Eskimos of the lower Kuskokwim River region.[5]

Osborn, Noriskin and Staz,[6] working among the Bantu of South Africa, exposed extracted undecayed teeth in vitro to saliva mixtures of crude cane sugar and sucrose for from two to eight weeks and found that with the refined sugar the teeth showed a great amount of decalcification, while with the crude sugar they showed only slight decalcification. They noted that the acidity of the solutions in the different tubes was the same throughout the duration of the experiment and concluded that there must be some other factor present which would account for the difference in the decalcifications. Further study [7] led them to the belief that a protective agent is present in sugar in the natural state which is removed during the process of refining.

The present work was carried on in three native settlements on the lower Kuskokwim River area. While all three villages were fairly close to a large white settlement, little visiting was done to the trading stores, and, when done, could be ascertained. For this reason, no attempt was

---

2. Rosebury, T., and Waugh, L. M.: A Study of Dental Caries Among Eskimos of the Kuskokwim Area in Alaska: I. Clinical and Bacterial Findings, Am. J. Dis. Child. **57**:871 (April) 1939.

3. Waugh, L. M.: Nutrition and Health of the Labrador Eskimos with Special Reference to the Mouth and Teeth, J. Dent. Research **8**:428 (June) 1928.

4. Waugh, L. M.: A Study of the Nutrition and Teeth of the Eskimo of North Bering Sea and Arctic Alaska, J. Dent. Research **10**:387 (June) 1930.

5. Waugh, L. M.: Dental Observations Among Eskimo: VII. Survey of Mouth Conditions, Nutritional Study, and Gnathodynamometer Data, in Most Primitive and Populous Native Villages in Alaska, J. Dent. Research **16**:355 (Aug.) 1937.

6. Osborn, T. W. B.; Noriskin, J. N., and Staz, J.: Comparison of Crude and Refined Sugar and Cereals in Their Ability to Produce in Vitro Decalcification of Teeth, J. Dent. Research **16**:165 (June) 1937.

7. Osborn, T. W. B.; Noriskin, J. N., and Staz, J.: Inhibition of in Vitro Decalcification in Teeth, J. Dent. Research **16**:545 (Dec.) 1937.

made to assure isolation of the natives concerned in the experiment. If such an attempt had been made, it is probable that the work would have ended in failure, for the natives would not have tolerated any sort of confinement for so long a period. Two of the towns had one small trading store each, but with the cooperation of the white owners of these stores we were able to maintain a close check-up on the purchase of sweets during the period of study. The third town had no store of any kind. The first two towns mentioned are Oscarville and Napakiak; the third, Naposkiak.

During the survey, data as accurate as possible were collected regarding the normal sugar and flour intake of the people. To this end, the traders who sell these products to natives were questioned as well as the natives themselves. While the information thus gained was of necessity indefinite, owing to the migratory life of the natives, it did show that even the primitive Eskimos had been getting some small amounts of refined wheat flour and sugar for about thirty to thirty-five years. However, all attempts to link the amounts of flour and sugar purchased with the presence of caries were generally unrewarded. This failure was probably due to the fact that the amounts consumed by the individual Eskimo were small. Bread was made by mixing the flour with water and a little salt and baking the dough in a pan. The result was a brown-surfaced bread about ½ inch (1.3 cm.) in thickness. Sometimes a small amount of baking soda, if available, was added, causing the mixture to rise to a thickness of about 1 inch. The bread was eaten in very small amounts, one loaf lasting a family of four or five about a week. The Eskimos do not have bread all year, as only after a successful hunting and trapping season are they able to purchase the flour, and that purchase includes only as much as the success of their "catches" permits. Generally the average family has enough to last only through January or February, and they do not restock until late summer or early fall. The sugar is not used as the white man uses it. The Eskimos make a native candy by browning the sugar dry, then adding water and boiling it down. The result is similar to a hard maple sugar, yellowish brown and about ⅛ to ¼ inch (0.3 to 0.6 cm.) thick. Very few of the natives dissolve this in their tea, in the cup; most of them place a small piece in their mouth while drinking the tea and allow the tea to dissolve the surface as it passes over. One small piece may last an Eskimo for two or three cups of tea. An attempt was made to link this habit with the presence of caries by questioning individual natives closely as to how long they had been using sugar in this way, how often they had the candy, and how long it was retained in the mouth. However, no connection was shown between this use of sugar and the incidence of caries. The amounts of sugar purchased, as related by the traders, varied a great deal. One

native might purchase as much as 100 pounds (45 Kg.) at one time, but this was for his whole family, including "in-laws" and dependents, which usually meant about 15 persons. One hundred pounds was the highest amount recorded, the average being around 50 to 60 pounds (23 to 27 Kg.) per year for a family.

PROCEDURE

The routine procedure of the present work was to examine the mouth and teeth with a mouth mirror and a finely sharpened explorer, charting all caries and "catches" on an individual sheet. Caries was indicated by a soft, pulpy feeling when the explorer touched definitely decayed matter and when it was possible to see the grayish blue tinge of undermined enamel. A "catch" was indicated by definite entrance of the point of the explorer into a pit or a break in the surface of the enamel. In the original examination, natives with mouths free from caries were mostly sought, but many were taken whose teeth presented a slight amount of decay. Immediately after the examination, a saliva specimen was taken. This was treated according to the method of Bunting and Jay of the University of Michigan:

1. Paraffin-stimulated saliva, 1 cc., was mixed with 4 cc. of broth (meat infusion, 1 per cent dextrose, p_H 5).

2. Of this mixture, 0.1 cc. was streaked on a Petri dish medium of tomato juice agar.

3. Both broth and plate were incubated four days at 37.5 C.

4. Slides were made from both of these, stained according to the method of Gram, with carbolfuchsin as a counterstain, and examined microscopically.

5. Results were charted separately on specially mimeographed sheets, and no comparisons were made until after the whole work had been completed.

At the conclusion of the original examination and collection of saliva, each native was allowed to choose the sweet which he or she wished to eat. As the experiment was to continue over an extended period and the cooperation of the subjects was an essential factor to the continuance of the work, they were allowed their choice, but close observation was necessary to see that the foods were approximately equally distributed in each settlement. In only a few instances was it necessary to insist that some subjects take assigned foods. After the selection of the sweets had been made, the subjects were fed a definite quantity each day. The amount was not sufficient to interfere in any way with their native diet or food intake. Each feeding was organized and closely supervised by both or either of the authors and the technician, or by the technician, to see that each native ate only his own food and that he ate all of it.

The foods containing natural sugars were given in the following amounts daily: 100 Gm. of raisins, dried figs or dates; 70 Gm. of pure maple syrup or honey. The foods containing refined sugars were given in the following amounts daily: 3 figs with juice preserved in 65 per cent of cane sugar; a 5 cent size chocolate candy bar of a well known brand, sticky, soft and chewy; 1 small round lollypop, different flavors; 6 sugar cubes, chewed but not rinsed, or a sugar solution consisting of 6 cubes dissolved in a cup of water and rinsed immediately.

The feeding periods of the people varied from five to thirteen weeks, but practically all of the periods were of five and one-half weeks' duration.

The authors feel that a record of the work and the conclusions drawn therefrom are best shown by the tables which follow

TABLE 1.—*Incidence of Caries and Lactobacilli in the Mouths of Eskimos Fed Refined Sugar*

Food	Subject	Weeks of Feeding	Feedings	Caries at Start	Caries at End	Lactobacilli		
						At Start	At Two Weeks	At End
Figs (preserved)...	A. E.	5	25	0	8	No	Yes	Yes
	N. S.	5	30	4	15	Yes	Yes	Yes
	N. M.	5	28	3	5	No	Yes	Yes
	O. W.	5½	24	0	0	No	Yes	Yes
	N. O.	5½	19	0	5	No	....	....
Candy bars.....	F. L.	5½	26	14	17	No	Yes	Yes
	M. A.	6	28	3	10	....	Yes	Yes
	J. M.	..	..	5	..	Yes	....	....
	E. J.	6	24	0	7	No	Yes	Yes
	W. M.	6	18	2	8	No	Yes	Yes
	S. M.* (see raisins)	5½	31	0	2	No	Yes	Yes
Lollypops.....	F. T.	5½	24	7	9	....	Yes	Yes
	S.	6	23	2 catches	7	No	Yes	Yes
	A. N.	5½	28	0	8	No	Yes	Yes
	S. S.	5½	26	0	4	No	Yes	Yes
	E. M.	5½	28	2	6	Yes	Yes	Yes
	A. J.	6	26	12 catches	20	No	Yes	Yes
	J. W.	10½	24	0	0	No	....	Yes
Sugar solution....	F. T.	5½ (see lollypops)		7	7	Yes	Yes	Yes
	Mr. N.	5½	28	0	0	Yes	Yes	Yes
	M. B.	5½	31	3	4	Yes	Yes	....
Sugar cubes.....	D. S.	5½	23	0	2	Yes	....	Yes
	M. S.	6	19	4 catches	4 catches	No	No	....
	S. T.	..	..	0	..	No	Yes	....

* This Eskimo was the interpreter. The first two weeks he was fed raisins, and the remainder of the summer, candy bars.

TABLE 2.—*Incidence of Caries and Lactobacilli in the Mouths of Eskimos Fed Natural Sugars*

Food	Subject	Weeks of Feeding	Feedings	Caries at Start	Caries at End	Lactobacilli		
						At Start	At Two Weeks	At End
Raisins.....	E.	..	..	0	..	No	....	....
	J. N.	5½	27	2	6	....	Yes	Yes
	S. M.	2	14	0	0	No	No	....
	M. N.	5½	27	9	10	Yes	Yes	Yes
	A. K.	5½	23	0	0	No	....	No
	Mr. K.	5½	31	3	3	No	Yes	No
Dried figs.....	S. E.	13	56	0	0	No	No (5 wk.)	Yes
	V. E.	7	37	0	0	No	No	No
	D. W.	2½	14	0	0	No	No	....
	C. J.	5½	30	1 catch	1 catch	Yes	Yes	Yes
	K. F.	5½	30	5	8	Yes	Yes	Yes
	N. S.	5½	19	0	0	No	No	....
	W. E.	6	13	0	..	No	No	....
Maple syrup.....	Mrs. N.	5½	26	0	0	Yes	No	Yes
	N. A.	5½	27	0	0	No	No	No
	M. A.	5½	28	0	0	Yes	Yes	Yes
	H. J.*	13	38	0	11	No	No (6 wk.)	Yes
	A. W.	5½	25	1	4	Yes	....	Yes
Honey.....	E. A.	5½	23	1	1	Yes	No	Yes
	A. A.	5½	25	0	0	No	No	No
	M. F.	13	51	0	0	No	No	No
Dates.....	M.	13	49	0	0	No	Yes	Yes

* This subject admitted that he ate "lots of candy" during the four weeks when he went to Bethel in the mornings to chop wood for the missionaries.

TABLE 3.—*Amount and Distribution of Foods Containing Natural Sugars*

Foods Given	Daily Amount, Gm.	Feeding Period	Average Number of Feedings	Subjects Given Each Food
Raisins	100	5½ weeks	24.4	6
Dried figs, prunes	100	5½ to 13 weeks	28.4	7
Pure maple syrup	70	5½ weeks (1 was 13 weeks)	28.8	5
Pure honey	70	5½ weeks (1 was 13 weeks)	33.0	3
Dates	100	13 weeks	49.0	1

TABLE 4.—*Amount and Distribution of Foods Containing Refined Sugars*

Foods Given	Daily Amount	Feeding Period	Average Number of Feedings	Subjects Given Each Food
Preserved figs (65% sugar)	3 figs with juice	5-5½ weeks	25.2	5
Candy bar	1 bar	5½-6 weeks	25.4	5
Lollypop	1	5½-6 weeks	26.2	5
Cube sugar	6 cubes	5½-6 weeks	21.0	2
Sugar solution	6 cubes in water	5½ weeks	29.5	3

TABLE 5.—*Summary of Observations on Growth of Lactobacilli in Mouths of Caries-Free Eskimos After Addition of Natural and Refined Sugars to Diet*

Sugar Given	Subjects Without Lactobacilli at Start	Subjects With Lactobacilli		
		At Start	After 2 Weeks' Feeding	After 5 Weeks' Feeding
Natural	86.68%*	13.32%	16.66%	11.11%
Refined	81.82%	18.18%	88.00%	100.00%

* This finding corroborates results reported by L. M. Waugh and D. B. Waugh in 1935 and by Rosebury and L. M. Waugh in 1936.

TABLE 6.—*Summary of Observations on Dental Caries in Eskimos After Addition of Natural and Refined Sugar to Diet*

Sugar Given	Caries-Free Subjects Who Remained Caries Free at End	Caries-Free Subjects Who Showed Caries at End	Subjects with Caries at Start Showing Caries Increase at End
Natural	92.31%*	7.69%	57.16% (average increase of 1.57 cavities)
Refined	27.27%	72.73% (average of 3.6 cavities)	100% (average increase of 4.9 cavities)

* The percentage would have been 100 except for H. J. (table 2) who reported eating "lots of candy" during a four week period when he visited Bethel daily.

SUMMARY AND CONCLUSIONS

The figures show the group fed various foods containing refined sugar to have been higher in dental caries at the beginning. This discrepancy may be accounted for in the dropping out of several Eskimos as well as in the fact that, in order to promote the necessary good will, the subjects were allowed to choose their own sweets. The foods were not divided by settlements but distributed as equally as possible among the people of all three villages. In many cases husbands and wives or other members of the same family selected different sweets. The percentage of those free from caries in the one group was compared with the percentage free from caries in the other, and the carious average of one group was compared with the carious average of the other. The results for the two groups are so drastically different that the deductions therefrom must be accepted as strongly indicative.

Practically 100 per cent of those free from caries in the group fed natural sugars remained free from caries, and showed a drop from the original percentage with lactobacilli. Of those with carious mouths in this group, 57.16 per cent showed an increase in cavities, with an average increase of 1.57 cavities, which might be considered a normal increase for actively carious mouths. From these figures one may conclude that with the Eskimo natural sugars do not initiate or cause an increase in the growth of oral lactobacilli; neither do natural sugars initiate or cause an increase in dental cavities.

Of those free from dental caries in the group fed refined sugars, 72.73 per cent showed inception of caries, with an average of 3.6 cavities. Of those with carious mouths in the group fed refined sugars, 100 per cent showed an increase in cavities, with an average increase of 4.9 cavities, which must be regarded as an increase far above normal for a five or six week period. In the group fed refined sugar 81.90 per cent showed initiation of the growth of oral lactobacilli, and these organisms were present in 100 per cent of the mouths at the end of the feeding period. From these figures one may conclude that with the Eskimo refined sugars initiate and cause an increase in the growth of oral lactobacilli and that they also initiate and cause an increase in dental cavities.

This is the first recorded field work on the effects of natural and refined sugars on oral lactobacilli and dental caries among the Eskimos and must be regarded as preliminary.

ENURESIS IN NEGLECTED CHILDREN

ERWIN WEXBERG, M.D.
NEW ORLEANS

The association of enuresis and delinquency is known to every experienced psychiatrist as one of the typical syndromes of child psychiatry. Only rarely is the child referred to the physician because of his enuretic habit. Usually the complaint is truancy, stealing, lying or sex delinquency; and as a rule it is only after careful questioning that a history, or with older children a past history, of bed wetting is obtained.

The social and economic background of the majority of delinquent children is rather poor, and one has the impression that a large number of the children are illegitimate, even when accurate statistics are not at hand. As one searches for possible environmental factors to account for their behavior problems, one usually encounters the fact that they have been neglected or discriminated against or not loved at all. Although one leaves out of the question such physical causes of enuresis as spina bifida, defective innervation of the vesical sphincters and abnormal depth of sleep, the obvious association between enuresis and emotional neglect demands some explanation.

The psychoanalytic explanation which might be advanced for the association is fairly obvious. According to the psychoanalysts, enuresis represents libidinous satisfaction at the autoerotic level. Children who lack affection, according to this explanation, fail to develop beyond the autoerotic stage or to transfer their libido at the normal age. Enuresis is therefore continued as a substitute satisfaction until later childhood.

Such an argument would be far more suitable as an explanation for masturbation. The threat of castration, which is supposed to account for the fact that children in their "latency period" do not masturbate, probably plays an unimportant role in the behavior of neglected children, whose parents are not sufficiently interested in them to take the trouble to control their habits of masturbation by frightening them. Furthermore, it is not entirely unusual to find children who continue to masturbate, or who even begin to practice sex relations, while at the same time they continue to wet their beds. It therefore seems that enuresis can properly be considered as an equivalent of sexual activity only in the occasional case, if at all.

Again, automatic emptying of the bladder during sleep is an entirely normal function for a considerable period of the infant's life, certainly up to the first half of the second year, or the beginning of the third year. During this period the maturation of the cerebral centers and the cerebrospinal pathways, which at first is

From the Division of Neuropsychiatry of the Louisiana State University Medical Center.

sufficiently far advanced to make voluntary bladder control possible only while the child is awake, must progress further before cortical control can be exerted during sleep. Is it reasonable, therefore, to consider the normal enuresis of the infant as "libidinous?" Not unless one is also willing to label as "libidinous" every other physiologic function which the child exercises. It would be possible to do this, of course, but if one did, eventually the libido concept would be void of specific meaning.

Because of the association, which has already been pointed out, between the child's behavior and his peculiar social situation, it would seem more reasonable to assume that the solution of the problem lies in the direction of social psychology. Here again it must be remembered that voluntary bladder control, diurnal as well as nocturnal, constitutes a recent acquisition of the child's third year and is usually achieved by systematic education. It is probably the first major educational achievement, for most of his previous educational progress is accomplished by mere conditioning. A mechanical method of training is not easily effective in dealing with a function which is performed in a state of unconsciousness, and it would seem that the acquisition of nocturnal bladder control is the first educational step which must be achieved on the higher mental level in which wilful effort replaces the mechanism of conditioning. The child must be willing to keep his bed dry at night, and this conative attitude enables him to find, instinctively, ways and means to accomplish his desire.

One possible method consists in a planned decrease of the depth of sleep. The firm resolution not to wet his bed keeps the child from sleeping too profoundly, just as one does not ever sleep as soundly as usual when one intends to wake up at a definite time. Because profound sleep is often the chief cause of enuresis, bladder control becomes much easier when the depth of sleep is reduced.

This method requires a strenuous effort on the child's part, and the question then arises as to what, in the normal course of events, causes him to make such an effort. There is little doubt that education is the underlying factor. Such education usually consists in disapproval, mild or strong, on the parents' part, whenever the child's bed is found wet and appreciation and praise whenever it is found dry.

The child promptly learns, in other words, that his social value depends in part on whether or not he has been able to control his bladder at night. Because he is not yet able to evaluate the importance of cleanliness for itself, education must substitute the social motive for the hygienic one. Cleanliness will henceforth assume the character of a social value, and the child will so regard it all of his life. Dirty children, just as dirty adults, meet with general contempt, and the child must face the same sort of contempt whenever his bed is found wet. The

effort necessary to train him in nocturnal bladder control is fed by his desire for social adequacy and his feeling of shame whenever he meets social disapproval. In short, the acquisition of perfect bladder control is one of the first steps in the development of social feeling.

Once this fact has been established, it is easy to account for the correlation between enuresis and neglect of the child. The parents' indifference deprives him of one essential motive in his development of social adequacy. Parental approval, the normal premium awarded a child for efforts made in the direction of social adjustment, is missing, and punishment is usually a sort of negative substitute. Whenever the child wets his bed, he is whipped, sometimes unmercifully. If the method is carried out ruthlessly, it is sometimes effective, in that fear of punishment supplies the motive for the child to make the effort required, but in the majority of cases it is unsuccessful.

One explanation of the failure may be that the child is whipped for so many other reasons that he becomes used to the punishment and no longer minds it. Another possible explanation is that the emphasis on a behavior pattern by punishment often contributes to preserving it rather than to destroying it. Once the child has grasped emotionally the connection between his enuresis and the punishment which follows it, the two experiences form a configuration, segregated from the rest of his experiences and with a dynamic content of its own. Punishment belongs to this closed configuration as an integral part of it, just as release and tension belong together.

It may be that in physicalistic terms (which should not, of course, be taken literally) punishment represents the "tension" side of the energetic system or "power field," with enuresis following as its necessary "release." The fact that punishment and misbehavior belong dynamically together and are interrelated with each other, as cause and effect, is not altogether new. Such a conception accounts for many of the observations of child behavior which are invariably characterized by the parents' puzzled statements, such as, "I can't tell you how often we have whipped him for that, and still he does the same thing over and over again."

It is hard to convince parents that the particular misbehavior, whether it consists of making faces, dawdling on the way to school, stealing or anything else, probably would end of itself if the punishment for it were discontinued. Yet this is often what happens. Once the vicious circle is broken, the misbehavior is likely to end of itself, though this does not, of course, always happen. There are instances in which the habit is being fed, so to speak, by the child's conative attitudes, which at a higher level make him continue his misbehavior for such reasons as to gain attention, to compensate for a brother's or a sister's

privileges or for a similar reason. In such cases the problem must be approached at the particular conative level involved, so that the child's desires, whatever they may be, may be satisfied in a less undesirable way.

It is true that the intricate overlapping of various configurations on various levels may also account for enuresis, but this is not necessarily true. Enuresis is usually not the result of something which the child wills to do, but rather the outward sign of something which he has failed to do, that is, to exert the effort to overcome it. This positive effort must be produced by the creation of a social system of reference which means enough to the child to make him actively contribute to it.

An enuretic child who has been shamed by his parents for any length of time for wetting his bed has usually so "lost face" that he no longer cares what his family thinks of him. On the other hand, if he is transferred temporarily to other surroundings, such as the home of an uncle, perhaps he may cease temporarily to wet the bed because the relative does not know of the habit. In an attempt to maintain honorable standing in the new environment, he makes the effort required and usually succeeds. The effort is rarely permanent, however, simply because the child's social self evaluation is not strong enough to make him continue the effort until the new habit has been formed. He probably feels that the honorable position granted to him by relatives, who do not really know him, does not correspond to what he really is, and he probably believes that he will not be able to maintain it. Once he has relapsed, the same old pattern will be re-formed in the new environment.

The considerable number of enuretic children in institutions and orphanages shows that institutional children very often are not given the emotional training which they need for social adjustment. The emotional requirements of children seem to show considerable individual variations, for reasons which cannot be fully explained. It is possible that the psychoanalytic explanation is correct and that experiences in early infancy determine later emotional needs. On the other hand, variations are found among children brought up in institutions from the first days of their lives. It may easily be, therefore, that a child's requirement for affection is determined by some unknown constitutional factor, which forms part of his innate temperament.

The practical conclusions of this point of view are simple. Such a habit as bed wetting is likely to be continued indefinitely because of the "repetition compulsion" inherent in every configurational pattern. This compulsion is probably nothing more than an integral part of configurational patternized behavior on a more primitive level of integration. In every configuration the well known factor of regularity, whether it is in visual *Gestalten* or in auditory or motor ones, involves iteration at regular intervals of time or space. It is natural, therefore, to assume

that a behavior pattern should repeat itself periodically, even without any specific dynamic factor to account for it, merely as the result of the intrinsic trend of regularity which makes a person integrate elementary patterns into more complex ones, following a compulsory tendency toward progressive organization. This is what Freud has called "repetition compulsion." Regularity, in other words, is the rule, and discontinuance of a habit can be achieved only by specific interfering factors.

Since this is true, undesirable behavior patterns must be altered only by some sort of shock, the word being used in its largest sense. By shock is understood any experience which is intense enough and profound enough to break a habit. It does not need to be a single experience, limited as to time. It may be a series of identical shocks, or it may be a complete change of living conditions. It is always possible, apparently, to obtain temporary success in the treatment of enuresis by any sort of shock, such as faradism, a severe punishment of unusual character, or a temporary or permanent change of environment.

But no sort of shock treatment can produce permanent results on enuresis if the dynamic factor in the treatment of neglected children is lacking, a social incentive to make the effort to overcome the habit. Even if success should be achieved by such a method, one would merely have removed the symptom without changing the pattern of maladjustment which underlies it and which accounts for many other undesirable traits of the personality of the neglected child. A more fundamental change of attitude is required, which will control the enuresis and the rest of the child's behavior troubles at the same time.

For such children is advocated removal into an environment likely to give them what they have failed to get heretofore and what they may legitimately claim: love, attention and keen interest in their welfare. Foster parents must be found who are willing and able to supply the emotional values which the child needs and who, at the same time, are intelligent enough to understand the child's predicament: his utter lack of self esteem because of his lack of appreciation in his previous environment; his "I don't care" attitude regarding social values, including cleanliness and sphincter control, and the hopelessness underlying the attitude, which has made him choose the line of antisocial success merely because social accomplishment seemed to be unattainable anyway.

In the guidance of these children, just as in child guidance in general, the emphasis must be put on the change of environment, though the older the child grows the more important will direct treatment become. Direct treatment consists chiefly in careful and systematic reeducation of the child and in reestablishment of the child's self esteem, as well as in utilization of those residuals of social ambition which are usually to be found even in children having the most serious enuretic habits.

The psychiatrist himself is the person most likely to become the child's partner in his newly established system of social reference. What in psychoanalytic nomenclature is usually called "transference" consists merely in the child's natural attachment to a person who apparently respects and appreciates him, while at the same time he is fully aware of all the shortcomings, errors and sins which darken his record.

With older children, everything depends on whether or not this psychologic operation which is attempted by the psychiatrist is or is not successful. If it fails, the child will make fun of the psychiatrist, whom he will consider a "sap," merely because he does not treat him with the same contempt and stern discipline to which he is accustomed. Such a failure may be due to deficient skill on the psychiatrist's part or to the stage to which the child's social waywardness has advanced or perhaps to both. Once the child is entrenched in this attitude toward the psychiatrist (it is precisely similar to the attitude many adult criminals adopt in response to the kindness of clergymen or of idealists among the wardens), no success with any method can be expected. He may outgrow his enuresis, as most children do when they grow up, but his basically asocial or antisocial behavior pattern will become more and more rigid.

Every patient, whether he is a child or an adolescent, is worth an attempt at psychiatric cure. Furthermore, since reformatories and prisons contribute a large number of the total of uncured children, as do orphanages, enuretic children and adolescents living in such institutions should be promptly removed from them. The very fact that a child has kept the habit for years in an institution proves that in it he does not obtain the degree of love, interest and attention which he requires for his social adjustment. This is not necessarily the fault of the institution, because, as I have pointed out, the emotional requirements of all children are not the same. Only when the number of enuretic children is definitely higher than the average is the conclusion warranted that something is wrong with the particular institution. Educational reform programs for orphanages and children's homes might well use the ratio of enuretic children to the total population as one index, among others, of the competency of the persons in charge.

CONCLUSIONS

1. Enuresis occurs frequently in neglected children who also exhibit social and antisocial behavior patterns.

2. The association of enuresis and neglect can be explained by the fact that the acquisition of nocturnal bladder control is part of every child's social training and that defective social training due to neglect therefore accounts equally for the enuresis and the antisocial behavior.

3. Treatment consists in the establishment of a normal emotional relationship between the child and his environment. This may be accomplished by a change of environment or by direct treatment or by both.

4. Particular attention should be paid to the incidence of enuresis in orphans' homes and in similar institutions. An unusually high incidence may be interpreted as resulting from the emotional starvation of individual children or even of the majority of the children living in such institutions.

TREATMENT OF PNEUMONIA BY SULFAPYRIDINE AND BY HYDROXYETHYLAPOCUPREINE DIHYDROCHLORIDE

MAUD L. MENTEN, M.D., PH.D.

ROBERT R. MACDONALD, M.D.

AND

NATALIE BRÖNYKOVSKY, B.S.

PITTSBURGH

The treatment of pneumonia by chemical compounds of known composition specifically adapted to inhibit the growth and the activity of the pneumococcus is a recent development of therapeutics. Quinine and its modifications were among the first of such drugs to be tried. In 1917 Moore and Chesney [1] and in 1919 Solis-Cohen [2] employed the quinine derivative ethylhydrocupreine hydrochloride in the treatment of pneumonia with some degree of success. This success was offset, however, by the toxic action of the drug on the visual apparatus. Maclachlan and his associates,[3] in a study of a number of modifications of quinine

---

Merck & Co., Inc., furnished the sulfapyridine used.

From the Department of Pediatrics and the Department of Pathology, University of Pittsburgh, and the Children's Hospital of Pittsburgh.

1. Moore, H. F., and Chesney, A. M.: A Study of Ethylhydrocuprein (Optochin) in the Treatment of Acute Lobar Pneumonia, Arch. Int. Med. **19**:611 (April) 1917; A Further Study of Ethylhydrocuprein (Optochin) in the Treatment of Acute Lobar Pneumonia, ibid. **21**:659 (May) 1918.

2. Solis-Cohen, S.: Present Status of the Definite Treatment of the Pneumonias, J. A. M. A. **73**:1741 (Dec. 6) 1919.

3. Maclachlan, W. W. G.; Permar, H. H.; Johnston, J. M., and Kenney, J. R.: Some Effects of Quinin Derivatives in Experimental Pneumococcus Studies, Am. J. M. Sc. **188**:699 (Nov.) 1934. Dawson, W. T.; Permar, H. H.; Johnston, J. M., and Maclachlan, W. W. G.: An Experimental Study of the Variations in the Production of Visual Disturbance by Certain New Cinchona Derivatives, ibid. **193**:543 (April) 1937. Maclachlan, W. W. G.; Permar, H. H.; Johnston, J. M., and Burchell, H. B.: Clinical Observations on the Treatment of Pneumonia and Empyema by Some Quinine Derivatives, Especially Hydroxyethylapocupreine, ibid. **194**:474 (Oct.) 1937. Johnston, J. M.; Burchell, H. B.; Permar, H. H., and Maclachlan, W. W. G.: Further Experiments on the Effect of Certain Quinine Derivatives on the Pneumococcus, J. Pharmacol. & Exper. Therap. **61**:364 (Dec.) 1937. Maclachlan, W. W. G.; Johnston, J. M.; Bracken, M. M., and Crum, G. E.: The Treatment of Pneumococcic Pneumonia by Hydroxyethylapocupreine, Am. J. M. Sc. **197**:31 (Jan.) 1939.

prepared for them by the Mellon Institute of Pittsburgh,[4] found experimentally that one of these—namely, hydroxyethylapocupreine—had a high pneumococcidal activity both in vitro and in mice and did not cause blindness. Subsequently, Maclachlan and his associates[5] reported its beneficial effect clinically in a number of cases of pneumonia. During the winter of 1937-1938 we made a preliminary study of the value of this drug in the treatment of pneumonia in children.

The introduction of sulfanilamide as a therapeutic agent which was highly effective in the treatment of hemolytic streptococcic infections but effective to a lesser degree in pneumococcic infections (as recently reviewed by Whitby[5]) gave impetus to the search for a more potent pneumococcidal agent. A notable addition to the list of antipneumococcic drugs is that of sulfapyridine by Whitby.[5] Already a number of reports attest its value in the treatment of this disease in adults and MacColl,[6] Evans and Gaisford,[7] Barnett and his co-workers,[8] Mitchell and his associates[9] and Hodes and his co-workers[10] have added claims for its action against pneumonia in children.

In this report an attempt is made to compare the therapeutic effects of sulfapyridine with those of hydroxyethylapocupreine dihydrochloride and to compare both of these with the effects of symptomatic treatment alone, as seen in a comparable group of control cases.

METHODS OF STUDY

The general incidence of pneumonia in the Pittsburgh district last year was low, and only about 30 per cent of the average annual number of patients with pneumonia was admitted to the Children's Hospital during the winter of 1938-1939. Furthermore, the infection was compara-

4. Butler, C. L.; Renfrew, A. G.; Cretcher, L. H., and Souther, B. L.: Cinchona Alkaloids in Pneumonia: IV. Derivatives of Ethylapocupreine, J. Am. Chem. Soc. **59**:227, 1937.

5. Whitby, L. E. H.: Chemotherapy of Pneumococcal and Other Infections, Lancet **1**:1210 (May 28) 1938.

6. MacColl, W. A.: Clinical Experience with Sulfapyridine, J. Pediat. **14**: 277 (March) 1939.

7. Evans, G. M., and Gaisford, W. F.: Treatment of Pneumonia with 2 (*p*-Aminobenzene Sulfonamide) Pyridine, Lancet **2**:14 (July 2) 1938.

8. Barnett, H. L.; Hartmann, A. F.; Perley, A. M., and Ruhoff, M. B.: The Treatment of Pneumococcic Infections in Infants and Children with Sulfapyridine, J. A. M. A. **112**:518 (Feb. 11) 1939.

9. Wilson, A. T.; Spreen, A. H.; Cooper, M. L.; Stevenson, F. E.; Cullen, G. E., and Mitchell, A. G.: Sulfapyridine in the Treatment of Pneumonia in Infancy and Childhood, J. A. M. A. **112**:1435 (April 15) 1939.

10. Hodes, H. L.; Stifler, W. C., Jr.; Walker, E.; McCarty, M., and Shirley, A. G.: The Use of Sulfapyridine in Primary Pneumococcic Pneumonia and in Pneumonia Associated with Measles, J. Pediat. **14**:417 (April) 1939.

tively mild, as indicated by the low mortality rate, especially that for the first twenty-four hours of hospitalization. Seventy-nine patients with pneumonia were treated; 74 of these were admitted from Jan. 1 to April 1, 1939. Data on 5 additional patients treated with sulfapyridine during the first two weeks of April have also been included. Because of the small number of cases and the high percentage of mixed infections among them, especially that associated with Haemophilus influenzae, it has been difficult to estimate the value of the drugs used. We are, therefore, presenting tabulated material rather than attempting to evaluate the results of statistical computations.

The 79 patients were divided into three groups according to the form of treatment used, namely, sulfapyridine, hydroxyethylapocupreine or symptomatic treatment. During the period of this study, as soon as a tentative diagnosis of pneumonia was made on admission of a patient to the hospital, the patient was assigned in rotation to one of the three groups. Cultures of material taken from the throat were made, and treatment was instituted immediately. If the tentative diagnosis was not subsequently confirmed, the patient was excluded from the group studied. In this way data were collected on 74 serial cases.

Because of the difficulty in obtaining sputum from children suffering with pneumonia, a technic was instituted for obtaining material for culture from the posterior part of the pharynx by hyperextending the child's head and depressing the tongue. Swabs were applied to this area, and coughing was elicited. The swabs were then incubated in hormone broth for six hours, after which they were stained by the Gram method and typed for pneumococci by the Neufeld technic. If no pneumococci were found, 1 cc. of the incubated broth was injected intraperitoneally into mice. In twelve or twenty-four hours the bacteriologic examinations were repeated on the intraperitoneal exudate. In some cases such oropharyngeal cultures, even when five or six swabs were incubated at varying intervals, failed to yield pneumococci. In cases in which H. influenzae was suspected to be present, chocolate agar plates were streaked. Because 70 per cent or more of the children under 2 years of age had otitis media associated with infection of the respiratory tract, cultures of material from the middle ears of these patients were also made. Myringotomy was performed on ears not already draining, and material for culture was taken by a technic designed to avoid contamination by the organisms residing in the skin of the auditory canal. The result of such bacteriologic cultures will be published separately.

Blood cultures were made in only about 60 per cent of the cases, as our previous studies indicated that children with pneumonia have an incidence of positive blood cultures of less than 6 per cent.

TABLE 1.—*Effects of Treatment with Sulfapyridine of Pneumonia in Patients Two Years of Age or Under*

Age, Mo.	Sex	Race	Lobes Involved*	Days Between Onset and Treatment	Type of Pneumococcus	Other Organisms	Temperature at Beginning of Treatment, F.	Days of Treatment	Total Amount of Drug Given, Gm.	Days of Treatment Before Normal Temperature	Results	Complications	Reactions to Drug	Red Blood Cells in Millions	White Blood Cells in Thousands	Blood Culture
Subgroup A																
8	F	W	L.L.L.....	1	III	.....	105.8	2	2.6	1	Cured	O.M.B.†	Vomiting	3.5	16.8	Not made
6	F	N	U.R.L.....	3	XIX	.....	105.2	6	8.5	2	Cured	O.M.B.	Vomiting, cyanosis	3.3	22.8 10.9	Negative
24	M	W	U.L.L., U.R.L.	½	II	.....	103.8	3	4.3	2	Cured	None	None	3.9	11.9	Negative
11	M	N	U.R.L.....	3	XIV	.....	103.0	3	3.6	2	Cured	None	None	3.3	16.6	Not made
8	M	W	U.L.L.....	½	Not found	Staph. aureus	105.0	5	5.3	3	Cured	O.M.B.	None	3.5	11.7 9.3	Negative
10	M	W	U.R.L.....	1	XX	.....	103.4	4	6.5	4	Cured	O.M.B.	Vomiting, cyanosis	3.5	29.4 9.8	Negative
12	M	N	U.R.L.....	3	Not found	.....	104.1	4	6.6	4	Cured	O.M.B.	Vomiting	3.2	8.3 9.8	Negative
15	M	W	U.R.L.....	6	Not found	.....	102.5	5	9.0	5	Cured	O.M.B.	Vomiting, cyanosis	3.5	10.5 7.2	Negative
8	M	W	U.L.L., U.R.L.	1	Not found	Staph. aureus	103.6	9	16.3	5	Cured	O.M.B.	Vomiting, cyanosis	3.2	8.9 7.7	Not made
4	F	N	U.L.L., U.R.L.	3	Not found	.....	104.4	7	13.0	5	Cured	O.M.B.	Vomiting, cyanosis	3.4	9.8 9.1	Negative
6	F	N	U.L.L., U.R.L.	1	VI	.....	102.8	5	9.3	5	Cured	None	Vomiting	3.1	20.8 11.9	Not made
Subgroup B																
7	M	W	H.L.L., H.R.L.	0	VI	H. influenzae	104.2	10	19.0	14	Cured	O.M.B.	Vomiting	3.6	12.2 9.7	Not made
9	M	W	L.L.L., U.R.L.	?	Not found	H. influenzae	101.0	4	7.7	14	Cured	None	Vomiting	3.3	13.0 11.5	Negative
12	M	W	U.L.L., U.R.L.	5	Not found	.....	105.2	6	10.6	7, 9, 10, 11	Cured	O.M.B.	Vomiting	3.1	20.4 6.9	Negative
7	F	W	L.R.L.....	2	XIX	H. influenzae, Staph. aureus	103.0	9	19.0	4, 12, 15	Cured	O.M.B.	Vomiting	3.3	20.0 13.3	Negative
16	F	W	U.L.L., U.R.L.	1	III, XIV	Staph. aureus	103.3	3	4.3	2, 9	Cured	D.M.B.	Vomiting	3.7	8.9	Not made
Subgroup C																
16	F	W	L.L.L.....	3	Not found	.....	105.0	8	16.3	..	Died	O.M.B.	Vomiting	3.4	9.7 17.7	Negative

* L.L.L. indicates the lower lobe of the left lung; L.R.L., the lower lobe of the right lung, U.L.L., the upper lobe of the left lung; U.R.L., the upper lobe of the right lung; H.L.L., the hilus of the left lung; H.R.L., the hilus of the right lung; M.R.L., the middle lobe of the right lung; Med., the mediastinum.
† Otitis media, bilateral.

TABLE 2.—*Effects of Treatment with Sulfapyridine of Pneumonia Patients Over Two Years of Age*

Age, Yr.	Sex	Race	Lobes Involved*	Days Between Onset and Treatment	Type of Pneumococcus	Other Organisms	Temperature at Beginning of Treatment, F.	Days of Treatment	Total Amount of Drug Given, Gm.	Days of Treatment Before Normal Temperature	Results	Complications	Reactions to Drug	Red Blood Cells in Millions	White Blood Cells in Thousands	Blood Culture
Subgroup A																
8	F	N	L.R.L.....	4	IV	Staph. aureus	105.2	4	10.0	1	Cured	None	Vomiting	3.2	19.8 12.8	Negative
10	M	N	U.L.L., L.L.L.	2	Not found	.....	104.6	5	11.7	2	Cured	None	None	3.4	20.5 7.0	Negative
7	M	W	L.L.H., H.L.L.	0	XIV	Staph. aureus	104.8	4	9.7	2	Cured	None	Vomiting	3.4	6.0 5.0	Not made
3	M	W	H.L.L., H.R.L.	2	XIII, graup E	.....	104.0	7	12.2	2	Cured	None	Vomiting, dyspnea	3.4	10.3 8.2	Negative
8	M	W	U.L.L., L.L.L.	1	Not found	.....	103.8	4	4.5	2	Cured	None	Vomiting, nausea	4.5	11.5 8.7	Not made
2	M	W	U.R.L.....	2	Not found	.....	103.2	4	9.5	2	Cured	O.M.B.†	Drowsiness	3.1	10.0 9.8	Negative
4	M	N	U.R.L.....	3	Not found	.....	104.8	4	13.0	2	Cured	None	Vomiting	3.3	19.8	Not made
4	F	W	U.L.L., U.R.L.	4	I	.....	104.8	3	3.4	3	Cured	O.M.B.	None	3.4	17.2 9.9	Negative
2	M	W	H.L.L., H.R.L.	3	XIV	.....	103.7	6	5.7	3	Cured	O.M.B.	None	3.8	9.5 7.3	Negative
4	M	W	L.R.L.....	5	XIV	.....	105.0	4	5.7	3	Cured	None	None	3.2	14.9	Negative
4	F	W	L.L.L.....	?	Not found	.....	105.0	4	9.5	3	Cured	None	Vomiting	3.6	26.2 12.9	Not made
8	F	N	U.R.L.....	1	I	.....	104.7	3	6.7	3	Cured	Pharyngitis	Vomiting, cyanosis	4.1	24.0 5.6	Negative
5	M	W	M.R.L.....	2	II	.....	104.2	5	19.5	4	Cured	Otitis media left err	Vomiting, nausea	3.5 4.0	16.8 13.8	Negative
Subgroup B																
6	F	W	L.L.L.....	2	I	.....	104.0	8	26.0	10	Cured	None	Vomiting, nausea	3.5	12.2 19.3	P., type I
6	F	W	M.R.L.....	8	I	Staph. aureus	107.0	7	17.3	8 (16)‡	Cured	None	Vomiting, nausea	3.6	20.6	P., type I, Staph. aureus

* See footnote to table 1.
† Otitis media, bilateral.
‡ The patient had been given sulfanilamide for eight days before treatment with sulfapyridine was begun.

TABLE 3.—*Effects of Treatment with Hydroxyethylapocupreine Dihydrochloride of Pneumonia in Patients Two Years of Age or Under*

Age, Mo.	Sex	Race	Lobes Involved*	Days Between Onset and Treatment	Type of Pneumococcus	Other Organisms	Temperature at Beginning of Treatment, F.	Days of Treatment	Total Amount of Drug Given, Gm.	Days of Treatment Before Normal Temperature	Results	Complications	Reactions to Drug	Red Blood Cells in Millions	White Blood Cells in Thousands	Blood Culture
Subgroup A																
23	M	W	U.L.L., U.R.L.	1	VIII	.....	102.2	3	5.3	1	Cured	O.M.B.†	None	4.1	5.7	Negative
12	F	W	L.L.L.....	0	V	.....	105.0	4	12.6	2	Cured	O.M.B.	Vomiting	3.0	18.2‡ 13.6	Negative
22	M	W	U.R.L.....	1	X, XXIX	Str. haemolyticus	104.0	6	7.6	3	Cured	.....	Vomiting	...	....	Negative
9	M	W	U.R.L., Med.	2	XIV	.....	105.0	3	9.0	3	Cured	.....	Vomiting, cyanosis	3.0	18.6 16.9	Negative
12	F	N	U.L.L.....	1	XX, group D	.....	104.0	2	4.0	4	Cured	O.M.B.	None	3.4	8.2	Not made
8	M	W	L.R.L.....	2	XVI	.....	105.0	5	9.3	4	Cured	O.M.B.	Vomiting	2.2	9.6 14.7	Negative
Subgroup B																
10	M	W	U.R.L.....	5	Not found	H. influenzae, Staph. aureus	104.0	6	8.6	15	Cured	Convulsions, O.M.B.	None	2.2	21.0 18.0	Negative
4	M	W	U.L.L., U.R.L.	1	Not found	Staph. aureus	102.0	9	19.3	2, 20	Cured	O.M.B.	Vomiting	3.0	10.7	Not made
20	F	W	L.L.L., L.R.L.	1	XIX	.....	103.0	19	38.3	14	Cured	O.M.B.	Vomiting	2.7	23.8	P., type XIX
Subgroup C																
10	M	W	U.R.L.....	4	XIV	H. influenzae	103.5	5	8.3	4	Died	O.M.B., rickets, malnutrition	None	2.8	24.2	Negative

* See footnote to table 1.
† Otitis media, bilateral.
‡ The first blood count was done at the beginning of pyrexia, the second at the end of pyrexia.

TABLE 4.—*Effects of Treatment with Hydroxyethylapocupreine Dihydrochloride of Pneumonia in Patients Over Two Years of Age*

Age, Yr.	Sex	Race	Lobes Involved*	Days Between Onset and Treatment	Type of Pneumococcus	Temperature at Beginning of Treatment, F.	Days of Treatment	Total Amount of Drug Given, Gm.	Days of Treatment Before Normal Temperature	Results	Complications	Reactions to Drug	Red Blood Cells in Millions	White Blood Cells in Thousands	Blood Culture
Subgroup A															
8	F	N	Right lung.....	3	XIV	101.7	3	15.0	1	Cured	Enlarged heart	Vomiting	2.0	11.7 10.8	Negative
7	M	W	L.L.L.....	1	Not found	104.0	7	17.0	2	Cured	None	Vomiting	3.5	9.6	Negative
7	M	W	L.R.L.....	7	V	104.0	3	13.3	2	Cured	Otitis media, left ear	None	3.9	19.5 17.9	Negative
7	F	W	L.L.L.....	2	Not found	105.0	3	16.0	2	Cured	None	Nausea; vomiting	3.7	10.4	Negative
3	M	W	L.L.L.....	3	Not found	105.0	7	15.5	2	Cured	None	Nausea; vomiting	3.1	26.6	Negative
6	M	W	U.L.L.....	4	X	104.5	4	9.6	3	Cured	None	Vomiting	3.4	17.8	Negative
5	F	W	L.L.L.....	4	XII, XXI	102.5	7	20.5	4	Cured	None	Vomiting	3.8	21.0	Negative
4	F	W	L.L.L.....	1	III	104.0	7	26.3	4	Cured	O.M.B.	Vomiting	3.6	15.2 13.6	Negative
9	M	W	Both lungs.....	3	Not found	103.3	2	8.5	5	Cured	O.M.B.	Vomiting	3.6	24.7	Negative
Subgroup B															
8	M	W	M.R.L.....	2	I	103.7	7	32.3	2, 10	Cured	None	Nausea; vomiting	3.9	17.6	Not made
3	F	W	Right lung.....	1	XIX	101.0	1	3.0	4, 18	Cured	None	None	4.4	14.6	Not made
5	F	N	U.R.L.....	7	V	105.2	5	7.0	2, 10	Cured	None	Nausea; vomiting	3.0	23.4	Not made
7	F	W	L.R.L.....	1	IV	103.4	3	10.6	2, 14	Cured	None	Nausea; vomiting	3.9	5.8	Negative

* See footnote to table 1.

TABLE 5.—*Effects of Symptomatic Treatment of Pneumonia in Patients Two Years of Age or Under*

Age, Mo.	Sex	Race	Days Between Onset and Admission	Lobes Involved*	Type of Pneumococcus	Other Organisms	Initial Temperature, F.	Days Before Temperature Reached Normal	Complications	Results	Red Blood Cells in Millions	White Blood Cells in Thousands	Blood Culture
						Subgroup A							
4	F	N	2	U.R.L.....	Not found	Staph. aureus	104.0	½	O.M.B.	Cured	3.4	6.7	Not made
16	F	W	0	U.L.L., U.R.L.	IX	.....	105.0	2	None	Cured	3.3	12.3	Negative
4	F	W	1	U.R.L., L.R.L.	XXIII	.....	104.0	3	O.M.B.	Cured	3.2	9.5	Not made
3	F	N	4	U.L.L., U.R.L.	XIII	.....	102.4	3½	None	Cured	3.2	6.1	Not made
18	M	N	2	U.L.L., U.R.L.	VI	.....	103.2	3½	O.M.B.	Cured	3.3	18.6	Not made
18	M	W	2	U.R.L.....	XIV	.....	103.0	4	O.M.B.	Cured	3.3	16.6	Negative
24	F	W	1	U.R.L.....	VI	.....	102.6	5	None	Cured	3.9	11.5	Not made
						Subgroup B							
13	M	W	1	M.R.L., L.R.L.	I	.....	104.8	9	O.M.B.	Cured	2.6	20.6 23.0	Not made
17	M	W	1	L.L.L.....	XXI	H. influenzae	103.4	2, 11	None	Cured	3.6	7.3	Negative
8	M	W	1	U.L.L.....	Group C	.....	104.0	3, 18	O.M.B.; vomiting	Cured	3.6	15.0	Not made
						Subgroup C							
12	F	W	1	Both lungs....	XIX	.....	104.0	..	Vomiting	Died	3.3	9.2	Negative
4	M	W	2	U.L.L., U.R.L.	XV	H. influenzae, Staph. aureus	102.0	5	Vomiting	Died	3.4	10.5	Negative
11	M	W	1	U.L.L., U.R.L.	Group C	H. influenzae, Staph. aureus	103.2	6, 11	Vomiting	Died	3.3	10.3	Not made

* See footnote to table 1.

TABLE 6.—*Effects of Symptomatic Treatment of Pneumonia in Patients Over Two Years of Age*

Age, Yr.	Sex	Race	Days Between Onset and Admission	Lobes Involved*	Type of Pneumococcus	Other Organisms	Initial Temperature, F.	Days Before Temperature Reached Normal	Complications	Results	Red Blood Cells in Millions	White Blood Cells in Thousands	Blood Culture
						Subgroup A							
4	F	N	0	U.L.L., U.R.L.	Not found	.....	104.2	½	None	Cured	...	....	Not made
4	M	N	2	U.R.L.....	VII	.....	102.2	3	Nausea; vomiting	Cured	4.0	19.1 9.5	Not made
3	M	W	2	U.R.L.....	VI, XV	.....	101.0	3	Nausea; vomiting	Cured	3.5	16.3	Not made
4	F	W	1	U.R.L.....	XXIII	.....	105.0	3	None	Cured	3.8	19.6	Not made
2	F	N	1	Both lungs....	X	.....	104.2	4	None	Cured	3.3	16.8	Not made
3	F	W	2	Both lungs....	VI	.....	103.7	5	Nausea; vomiting	Cured	3.1	13.5	Not made
3	M	W	5	L.R.L.....	Not found	.....	104.5	5	Nausea; vomiting	Cured	3.8	14.5	Not made
						Subgroup B							
6	F	W	2	H.L.L., H.R.L.	Not found	H. influenzae	105.8	2, 4, 7, 14, 16	O.M.B.; vomiting	Cured	3.8	12.7 16.8	Negative
11	M	W	3	L.L.L.....	VI	.....	101.4	2, 12, 16	Nausea; vomiting	Cured	4.4	17.5	Negative
3	F	W	1	U.L.L., right lung	XIV	.....	104.2	6, 10, 16	Nausea; vomiting	Cured	3.3	8.9	Negative
4	M	W	2	U.R.L., M.R.L.	XXIX	.....	103.0	5, 10, 12	Nausea; vomiting	Cured	3.1	12.3	Negative

* See footnote to table 1.

Addis counts were made for a number of older children from whom urine could be readily collected. Only one count showed red blood cells. This count, as well as those of the white blood cells and casts which were invariably present in moderate numbers, was of no pathologic significance.

Complete blood counts were made at the beginning of the treatment and subsequently as indication arose. White cell counts and determinations of hemoglobin were made during the course of the disease if the dosage of drug was high or the treatment was prolonged. The results of all physical examinations of the chest were confirmed roentgenographically. The course of the pneumonia was followed by repeated physical examinations supplemented by roentgen studies.

The data for each of the three groups of patients divided according to treatment are presented in the accompanying tables on the basis of age, namely, data for children of 2 years and under and those for children over 2 years of age. These patients were further divided into three subgroups as follows: A, those who responded readily to treatment; B, those whose recovery was delayed, and C, those who died.

No distinction has been made between clinical bronchopneumonia and lobar pneumonia. Roentgenograms indicated that practically all of the patients had bronchopneumonia. Extensive pathologic studies on a large volume of material obtained at autopsies over a period of several years indicate an exceedingly small percentage of alveolar pneumonia in children dying from pneumonia in the Children's Hospital.

The date of the onset of the disease, as indicated in the tables, was ascertained by the admitting physician from the patient and is obviously only approximately accurate. The complication most constantly observed was otitis media. The data for subgroup A of each group is arranged so that the duration of pyrexia in days is placed in an ascending order. This is used as a rough index of the efficiency of the drug in the treatment of pneumonia, because the mortality rate of the disease is low for children. The dosage of both sulfapyridine and hydroxyethylapocupreine has varied widely. With sulfapyridine, we have, in the main, followed the dosage recommended by Evans and Gaisford,[7] which is 0.15 Gm. every four hours for infants 1 to 3 months old and 0.9 Gm. for children of 12 years. Throughout the study the initial dose (and occasionally the second or the third dose) of both drugs has been doubled. Later in the course of treatment of any patient the dosage was invariably reduced and the interval between doses prolonged. Early in the study the chemotherapy was continued for several days after the temperature had fallen to normal. This procedure was soon discontinued because of the prevalence of nausea and vomiting, which occurred with both drugs. This reaction disappeared readily on discontinuance of the sulfapyridine

but somewhat slowly with hydroxyethylapocupreine. In almost no instance was early discontinuance of either drug followed by a recurrence of fever.

Levels of sulfapyridine in the blood were not studied.

RESULTS

Pneumococci, varying widely as to type, were recovered on culture from 56 (70 per cent) of the 79 patients studied. In a great many of the cases in which pneumococci were not cultured, repeated incubation of oropharyngeal swabs were made, with negative results. Nonhemolytic streptococci were obtained from practically all oropharyngeal swabs and apparently had little pathologic significance.

As already stated, we have found it difficult to estimate the comparative value of the two drugs studied, mainly, we believe, because of the occurrence of secondary infection and especially because of the presence of H. influenzae.

Clinically, the patients included in each of the three groups readily fell into two subgroups, depending on the speed of recovery. In that subgroup in which the infection was apparently due to the pneumococcus alone, there was a speedy, dramatic fall of temperature to the normal level, followed by rapid recovery. In the second subgroup the increased temperature was prolonged for about two weeks and showed wide daily fluctuations (99 to 105 F.), regardless of the type of treatment. These patients were toxic and acutely ill. H. influenzae was not infrequently cultured from their oropharyngeal swabs, and when such organisms were not obtained the similarity of the temperature curve and the clinical course of the disease led one strongly to suspect their presence. Staphylococcus aureus was also a secondary invader. The possible presence of the influenza virus and its role in the prolongation of the pneumonia are matters of conjecture. It is possible also that the delayed resolution (up to five and six days) in some cases in which the pneumonia was supposedly caused by the pneumococcus alone may have been due to the presence of small numbers of H. influenzae.

Because of mixed infection in some of the cases we doubt whether the three deaths in the control group as compared to one death in each of the other groups have much significance in the evaluation of specific treatment. Likewise of questionable significance is the computed value of two and nine-tenths days for average duration of pyrexia before a drop to normal in each of the treated patients, as against three and two-tenths days for the comparable controls. For this computation, only the data for those children who responded readily to treatment (subgroup *A*, II) and had mixed infection have been included.

For the children who responded to treatment by a fall in temperature within forty-eight hours, crisis was the rule. The fall of temperature was usually by lysis for those who recovered more slowly.

A decrease in pulse rate paralleled the drop in temperature in most cases, but the pulmonary involvement resolved more slowly, as indicated by roentgenograms. Those patients whose temperature responded promptly to treatment showed a rapid clinical improvement, which was most pronounced in the patients treated with sulfapyridine.

The most manifest evidences of toxic effect were in the gastrointestinal tract. Nausea and vomiting were frequently observed after the administration of both drugs. It should be noted, however, that vomiting frequently occurred in children before specific treatment as well as in those of the control group. Prompt relief followed discontinuance of the sulfapyridine, and these patients regained their appetites almost immediately. The gastric disturbances were more prolonged after the discontinuance of hydroxyethylapocupreine. This phenomenon was especially noted in younger children. Cyanosis, restlessness and irritability occurred with the use of sulfapyridine, as indicated in the tables. There was no evidence of jaundice, agranulocytosis or cutaneous rashes. Toxic manifestations of the hydroxyethylapocupreine were confined to gastric symptoms.

COMMENT

The difficulty of arriving at definite conclusions regarding the value of the specific treatments used for such a small number of children with pneumonia is evident. However, we feel that our experience taken in conjunction with the results of other workers may aid in the final evaluation of these drugs. Clinically, one gains a definite impression that the course of the disease is appreciably shortened when the causative organisms are limited to the pneumococci. With mixed infections, especially when H. influenzae is present, the value of both of the therapeutic agents under discussion is open to question and requires further study.

SUMMARY

The tabulated results of treatment of 32 children with pneumonia with sulfapyridine and of 23 with hydroxyethylapocupreine dihydrochloride are compared with the results of symptomatic treatment of 24 children.

Comparative evaluation of the data for the three groups is difficult because of the presence of mixed infection, including H. influenzae, in many of the cases.

ETIOLOGIC STUDIES OF SPORADIC CASES OF ENCEPHALITIS OCCURRING IN THE ST. LOUIS AREA IN 1938

MARGARET G. SMITH, M.D.

EDWIN H. LENNETTE, M.D.

AND

RUSSELL J. BLATTNER, M.D.

ST. LOUIS

During the summer and fall of 1938, 10 children were admitted to the St. Louis Children's Hospital with symptoms suggestive of some type of encephalitis. The clinical picture presented by these children was not uniform, but in each case there was evidence of cerebral involvement. In several instances (cases 1 to 6 in the accompanying table) the condition closely resembled St. Louis encephalitis manifested by children in 1933 and 1937. In 1 case (7) the clinical symptoms, although less definite, still simulated the milder form of this disease seen during the outbreak of 1937. The condition in another case (8) was suggestive of neuronitis. In case 9 the illness, which left striking residuals, was comparable to type A rather than to type B encephalitis, and in case 10 a tentative diagnosis of atypical polioencephalomyelitis was made.

Two other children (cases 11 and 12) observed during this period presented postencephalitic residuals. Each had had an acute illness diagnosed as encephalitis, in 1933 and in 1937, respectively. An interesting history was obtained concerning the second patient; a disease diagnosed as encephalitis had occurred in a horse in the neighborhood of the child's home shortly before his illness.

A relatively high percentage of serums from a somewhat similar but larger group of children observed in 1937 had been shown to contain neutralizing antibodies for the virus of St. Louis encephalitis.[1] In view of this experience the serums from the children in the 1938 group were also tested for antibodies for this virus. However, the doubtful origin of the disease or diseases suffered by these patients was only emphasized by the almost consistently negative results obtained with their blood in mouse protection tests with the virus. The possibility that

From the Department of Pathology and the Department of Pediatrics, Washington University School of Medicine and the St. Louis Children's Hospital.

1. Smith, M. G., and Moore, E.: J. Infect. Dis. **63**:319-323, 1938.

infections with the virus of equine encephalomyelitis had occurred was considered in view of the occurrence in New England of an outbreak of encephalitis due to the Eastern strain of this virus.[2] Lymphocytic choriomeningitis was also considered clinically as a possible diagnosis in 1 instance (case 1). Therefore, specimens of serum obtained from patients during the acute stage of their illness and in most instances also during convalescence were examined for neutralizing antibodies not only against the virus of St. Louis encephalitis but also against a western strain of the virus of equine encephalomyelitis and against the virus of lymphocytic choriomeningitis.

MATERIAL AND METHODS USED IN NEUTRALIZATION TESTS

Virus.—The Hubbard strain of St. Louis encephalitis virus isolated in 1937[3] was employed in the neutralization studies. The western strain of equine encephalomyelitis virus was supplied by Dr. A. B. Sabin, of the Rockefeller Institute for Medical Research, and the lymphocytic choriomeningitis virus by Dr. N. Paul Hudson, of the department of bacteriology of Ohio State University.

Source of Serum.—Specimens of serum were obtained from 19 children seen at St. Louis Children's Hospital during 1938. Ten of these children, ranging in age from 2 months to 13 years, had been admitted with clinical symptoms and findings suggestive of acute encephalitis. From 2 of these children samples of blood were obtained only early in the illness, on the second and the seventh day, respectively. From the other 8, samples were obtained at intervals of three weeks to eight months after the onset, in addition to a few earlier ones (table). Serums were also obtained from 2 children (cases 11 and 12), aged 5 and 8 years, respectively, who showed encephalitic residuals in 1938 when first seen. The remaining 7 serums, which served as controls, were obtained from children with illnesses other than encephalitis whose ages ranged from 2½ to 12 years.

Neutralization Tests.—Freshly removed mouse brains containing the virus were cultured and kept frozen until sterility was proved, usually for twenty-four hours. Two brains were pooled, weighed and made into a 10 per cent suspension with nutrient broth (p_H, 7.4). The supernatant, after light centrifugation for several minutes, was used to make serial tenfold dilutions. The dilutions used varied with the virus. In all cases, two parts of serum were mixed with one part of the virus dilution and incubated at 37 C. for two hours, after which the mixtures were injected intracerebrally in 0.03 cc. amounts into Swiss mice, 4 animals being employed for each dilution.

With the St. Louis encephalitis virus, dilutions of $10,^{-3}$ 10^{-4} and 10^{-5} were employed in making the virus-serum mixtures. These dilutions and the interpretations of the results of the neutralization tests with this virus were determined on the basis of criteria previously reported.[4] With the equine encephalomyelitis virus, dilutions of $10,^{-5}$ 10^{-6} and 10^{-7} were used, and with the lymphocytic choriomeningitis virus, dilutions of $10,^{-3}$ 10^{-4} and $10.^{-5}$ These dilutions were

2. Fothergill, L. D.; Dingle, J. H.; Farber, S., and Connerley, M. L.: New England J. Med. **219**:411, 1938.

3. McCordock, H. A.; Smith, M. G., and Moore, E.: Proc. Soc. Exper. Biol. & Med. **37**:288-290, 1937.

4. Muckenfuss, R.; Smadel, J. E., and Moore, E.: J. Clin. Investigation **17**: 53-57, 1938.

Case	Patient	Age	Race	Sex	Date of Onset of Symptoms	Symptoms and Findings	Cerebrospinal Fluid				Residuals	Interval Between Onset of Illness and Dates Samples of Blood Were Obtained
							Date Examined	Globulin Present	Total No. of Cells	Lymphocytes, %		
1	T. S.	2 mo.	Negro	M	8/ 5/38	Infection of upper respiratory tract; irritability; questionable cervical rigidity; maximum temperature 40 C. (104 F.)	8/12/38 8/15/38 8/17/37	+++ ++ +	1,100 165 380	87 95 98	None	1st sample, 20 days; 2d sample, 7 mo.
2	F. C.	12 yr.	Negro	M	6/13/38	Infection of upper respiratory tract; malaise; headache; vomiting; maximum temperature 40 C. (104 F.)	6/20/38	++++	120	95	None	1st sample, 7 days; 2d sample, 8 mo.
3	B. B.	8 yr.	White	F	7/29/38	Headache; cervical pain; severe nausea and vomiting; diminished deep reflexes; maximum temperature 37.6 C. (99.7 F.)	8/30/38	—	54	50	None	1st sample, 1 mo.
4	G. D.	4 yr.	Negro	F	8/10/38	Headache; severe vomiting; drowsiness; cervical rigidity; positive Kernig sign; maximum temperature 40 C. (104 F.)	8/11/38 8/17/38	+ +	600 150	98 99	None	1st sample, 2 days
5	J. P.	2 yr.	White	M	7/22/38	Convulsions; coma; meningeal signs; maximum temperature 39.8 C. (103.6 F.)	7/23/38 7/29/38	— +	162 22	20 10	None	1st sample, 1 mo.
6	B. W.	5 mo.	White	F	9/18/38	Convulsions; maximum temperature 38.5 C. (101.3 F.)	9/18/38	+++	560	88	Tendency toward convulsions with acute infections	1st sample, 5 wk.; 2d sample, 6 mo.
7	J. L.	6 yr.	White	M	8/17/38	Infection of upper respiratory tract; drowsiness; listlessness; maximum temperature 38.3 C. (100.9 F.)	8/22/38 12/28/38	— —	5 9	100 100	None	1st sample, 8 days; 2d sample, 2 wk.; 3d sample, 4 mo.
8	J. W.	2 yr.	White	F	4/ 8/38	Drowsiness; listlessness; inability to stand; maximum temperature 37.4 C. (99.3 F.)	4/10/38 4/11/38 4/15/38	± + +	21 457 11	100 75 100	None	1st sample, 1 wk.
9	W. C.	2 yr.	White	M	7/12/38	Convulsions; coma; generalized spasticity; maximum temperature 40 C. (104 F.)	8/ 3/38	+++	75	100	Generalized spasticity	1st sample, 3 wk.; 2d sample, 8 mo.
10	V. M.	1 yr.	White	F	7/16/38	Listlessness; stupor; generalized weakness; difficulty in deglutition; maximum temperature 37.6 C. (99.7 F.)	9/ 6/38	—	4	75	Fatigues easily	1st sample, 2 mo.
11	J. T.	5 yr.	White	M	9/ 1/38	Difficulty with speech; loss of memory and behavior disturbances in September 1937; maximum temperature 37.4 C. (99.3 F.)	10/13/38	—	3	100	Mental deterioration	1st sample, 14 mo.
12	D. N.	8 yr.	White	F	8/ ?/33	Acute illness diagnosed as encephalitis in 1933	.....	..	..	...	Marked tremors; difficulty in walking; deformities of legs and spine	1st sample, 5½ yr.

arrived at by determining the range over which known positive serums in duplicate tests neutralized in the aforementioned proportions. The neutralization tests in all instances were controlled by the inclusion of serums known to give negative or positive reactions.

RESULTS

All samples of blood, including the 7 control specimens, were tested for neutralizing antibodies against the virus of St. Louis encephalitis, and, with the exception of the serum of 1 patient, all showed their complete absence. The single exception (case 2) gave questionable neutralization with each of 2 samples obtained seven days and eight months, respectively, after the onset of the acute illness.

In carrying out neutralization tests against the virus of western equine encephalomyelitis and against that of lymphocytic choriomeningitis, when more than one specimen of blood had been secured from a patient only the most recent one was used. Without exception, all the serums failed to neutralize these viruses.

COMMENT

In considering the negative results of the neutralization tests against the virus of St. Louis encephalitis, it appears certain that this virus was not the etiologic agent for the condition of at least 7 of the 10 children seen during their acute illness. Samples of blood were obtained from these 7 children sufficiently long after recovery to warrant the assumption that antibodies to the causal agent would be present. The negative results obtained with serums from the patients in cases 4 and 8 remain of questionable significance, because in these 2 instances the blood was drawn only early in the course of the disease, at a time when the formation of antibodies might not have occurred.

The questionably positive neutralizations consistently obtained with the serum of 1 patient (case 2) both early in the disease and months later is open to more than one interpretation: The slight degree of neutralization obtained in the tests may have depended on infection with the virus at the time of the 1938 illness or may have depended on traces of antibodies acquired at some previous time. The fact that there was no increase in the titer of the neutralizing antibody at a late date over that present as early as the seventh day of the illness arouses doubt that the illness in question was responsible for the production of these antibodies. The child was 12 years of age at the time of the present illness and therefore had lived through two epidemics of encephalitis in St. Louis—presumably ample opportunity for exposure to the virus. That subclinical immunization to this virus occurs is indicated by the report of Muckenfuss, Smadel and Moore.[4] These authors found that approx-

imately 35 per cent of the adults living in St. Louis who gave no history of encephalitis possessed neutralizing antibodies for the virus of St. Louis encephalitis when their serum was tested after the epidemic of 1933.

Again, the entirely negative results obtained with the serums of the 2 children with postencephalitis residuals, whose illness occurred one year and five years before, respectively, is only presumptive evidence against this illness being due to the virus of St. Louis encephalitis. It is not impossible that the neutralizing antibodies may have disappeared in this interval. We have obtained evidence that the titer of the serum of patients having encephalitis in 1933 has dropped in some instances.

What the origin of the disease in this group of cases may have been remains a matter for speculation. The viruses of western equine encephalomyelitis and of lymphocytic choriomeningitis as well as that of St. Louis encephalitis seem to have been eliminated as etiologic agents. However, this group of cases serves to emphasize the sporadic occurrence of encephalitis of unknown character. The records of the St. Louis Children's Hospital as analyzed by Dr. Alexis F. Hartmann [5] reveal that cases in which a diagnosis of encephalitis was made in the fourteen years preceding the epidemic of 1933 had shown a definite seasonal incidence. The increase began in June, reached its peak in July and August and began to decline in August and September. After the spectacular epidemic of the summer of 1933, the question was raised whether the somewhat similar cases occurring in previous years had been instances of the same condition. Cases such as those observed in 1938, in which tests for neutralization gave evidence against the St. Louis encephalitis virus as an etiologic agent, only make that question more difficult to answer.

That occurrences of this sort are not limited to St. Louis is emphasized by the following incident. While the present study was in progress, an outbreak of encephalitis occurred around Minot, N. D., several cases terminating fatally. Since there had been encephalomyelitis among the horses of that area, serum [6] which we obtained from 4 patients from that locality was tested against the virus of equine encephalomyelitis as well as against the viruses of St. Louis encephalitis and of lymphocytic choriomeningitis. In no instance did these serums neutralize either the virus of equine encephalomyelitis or that of lymphocytic choriomeningitis. As regards the virus of St. Louis encephalitis, three of the serums failed to inactivate it, while the fourth on repeated tests gave equivocal results. We have no information as to the previous

5. Report on the St. Louis Outbreak of Encephalitis, Public Health Bulletin 214, United States Public Health Service, January 1935.

6. Dr. Paul J. Breslich and Dr. Garnett S. Seiffert of the Northwest Clinic at Minot, N. D., supplied us with material obtained during this outbreak.

place of residence of this patient and cannot judge the possibility of her having been exposed at a previous time to the virus of St. Louis encephalitis.

Material from the brain of a patient who died during this outbreak gave negative results when injected intracerebrally into mice, guinea pigs and monkeys.

SUMMARY

Serums from 10 children in the St. Louis area believed to have acute summer encephalitis and from 2 children with postencephalitic residuals dating to illnesses in the summer of 1933 and 1937, respectively, were examined for their antibody content against the viruses of St. Louis encephalitis, western equine encephalomyelitis and lymphocytic choriomeningitis.

All failed to neutralize the viruses of lymphocytic choriomeningitis and equine encephalomyelitis. Eleven of these serums likewise did not inactivate the virus of St. Louis encephalitis; the twelfth gave a questionably positive neutralization. The significance of these results is discussed.

Serums from 4 patients who had encephalitis during a small outbreak in North Dakota during the summer of 1938 also were tested against these viruses. They likewise failed to reveal the etiologic agent involved. Results of attempts to isolate a virus from the brain of a patient who died in this outbreak were negative.

TREATMENT OF PERTUSSIS WITH A DETOXIFIED ANTIGEN

NATHAN M. GREENSTEIN, M.D.
AND
WALTER LEVY, M.D.
NEW YORK

The treatment of pertussis has been a source of great disappointment. Of the numerous measures that have been recommended, none has proved entirely satisfactory. Various forms of vaccines have been utilized;[1] Haemophilus pertussis has been detoxified with heat, with solution of formaldehyde, with bactericidal substances and by mechanical disruption. Innumerable drugs have been tried, including, among the most recent, ascorbic acid[2] and sulfanilamide.[3] Alteration of the acid-base[4] balance has been suggested. However, the failure of the general acceptance of any of these measures indicates only too well their inadequacies.

One of the latest forms of therapy along immunologic lines is a toxic filtrate of H. pertussis which has been detoxified with solution of formaldehyde. This is not a vaccine, in that it is entirely free of bacterial cells and, so far as possible, free of autolytic products of bacteria. Neither is it similar to the mucoid substance prepared by Toomey.[5] This filtrate is prepared from H. pertussis cultures grown in shallow

From the Service of Dr. S. T. Levethan, Riverside Hospital.

1. (*a*) Frawley, J. M.; Stallings, M., and Nichols, V. C.: A New Pertussis Antigen, J. Pediat. **4**:179, 1934. (*b*) Madsen, T.: Whooping Cough: Its Bacteriology, Diagnosis, Prevention and Treatment, Boston M. & S. J. **192**:50, 1925. (*c*) Sauer, L. W., and Hambrecht, L.: Whooping Cough Vaccine Therapy, J. A. M. A. **91**:1861 (Dec. 15) 1928. (*d*) Bumbalo, T. S.: Treatment of Pertussis with the New York State Pertussis Vaccine, Am. J. Dis. Child. **52**:1390 (Dec.) 1936.

2. Ormerod, M. J.; Unkauf, B. M., and White, F. D.: A Further Report on the Ascorbic Acid Treatment of Whooping Cough, Canad. M. A. J. **37**:268, 1937.

3. Cruickshank, J. C.: Sulfanilamide and "M & B 693" in Experimental Pertussis in Mice, Lancet **2**:310, 1938.

4. Regan, J. C., and Tolstoouhov, A.: Relations of Acid Base Equilibrium to the Pathogenesis and Treatment of Whooping Cough, New York State J. Med. **36**:1075, 1936.

5. Toomey, J. A.: Newer Aspects of the Whooping Cough Problem, J. Pediat. **10**:472, 1937.

layers on special mediums. When it is injected into the skin of rabbits and human beings, it may produce swelling and erythema. When it is treated with solution of formaldehyde in the manner in which diphtheria toxoid is produced, the toxicity is reduced but the antigenic properties are retained. The nature of the immunologic reaction which leads to a cure by this antigen is not definitely understood. The antigen is certainly different in composition from the Krueger endotoxin, which has yielded good results in the hands of some investigators.[6] Evans and Maitland,[7] who studied various toxic extracts of H. pertussis, concluded that there was no perceptible difference in the antigenic properties of living bacilli, killed bacilli and the extracts made from them. Demnitz, Schlüter and Schmidt [8] used an antigen to produce an antitoxin in horses. They found there was no relation between an adequate toxin-neutralizing power and a low antibody titer.

In view of the failure of other forms of treatment, we decided to study the effectiveness of this new toxic filtrate to cure pertussis.

The antigen used in this investigation was several times stronger than the available commercial product. It was supplied through the courtesy of the Lederle Laboratories, Inc., and was prepared from individually selected cultures that were found to produce an unusually toxic filtrate. Laboratory tests showed that a dose of 0.5 cc. contained about four times as much antigen as the regular 2 cc. dose when this material was first distributed.

INVESTIGATION

The pertussis pavilion of the Riverside Hospital provided an opportunity to evaluate the efficacy of the detoxified antigen described previously. This study was performed under carefully controlled conditions. The building is composed of an east and a west wing, which are separated from each other by a corridor on each floor. Each ward of eight beds is divided into individual cubicles. Strict isolation technic was observed. The nurses were restricted to service in one ward during the entire study. A daily record was kept for each patient, on which were noted the frequency and the severity of the coughs, whoops and emeses. In addition, remarks pertinent to the clinical picture of each child were added daily. The east wing of the building was selected for the patients treated, and the west wing was utilized for the controls. The infants up to 1 year of age were on the

6. (*a*) Munns, G. F., and Aldrich, C. A.: Hemophilus Pertussis Endoantigen (Krueger): Use in One Hundred and Twenty-Two Cases, J. Pediat. **5**:590, 1934. (*b*) Stallings, M., and Nichols, V. C.: Treatment of Whooping Cough with an Active Undenatured Antigen, Am. J. Dis. Child. **48**:1183 (Dec.) 1934.

7. Evans, D. G., and Maitland, H. B.: The Preparation of the Toxin of Hemophilus Pertussis: Its Properties and Relation to Immunity, J. Path. & Bact. **45**:715, 1937.

8. Demnitz, A.; Schlüter, W., and Schmidt, H.: Ein antitoxisches Keuchhustenserum vom Pferd, Klin. Wchnschr. **15**:10, 1936.

first floor, and the other children occupied the second and third floors. Alternate patients were selected for treatment and for control on admission. Where there was any question as to the diagnosis of pertussis, the patient was eliminated. There remained a total number of 135 children who were admitted between June 1, 1938 and Oct. 1, 1938. None of these children had received any prophylactic immunization prior to their admission. Sixty-five of them received treatment, and 70 served as controls. The doses of the antigen varied with the ages of the patients and were administered subcutaneously every other day for five injections. The original dosage for the infants was 0.2, 0.4, 0.6, 0.8 and 1.0 cc. This was subsequently increased to 0.4, 0.6, 0.8, 1.0 and 1.0 cc. repeated. The older children received the latter dosage from the start. The disease was classified as mild, moderate and severe. This classification represented a weekly summary of the clinical manifestations based on the careful daily enumeration of the frequency and the severity of the coughs, whoops and emeses. Since the patients who were treated received a series of five injections, ten days elapsed from the time of a child's admission to the completion of the treatment. The effect of the treatment was observed two weeks after the beginning of the injections.

TABLE 1.—*Case Incidence of Pertussis in New York City*

Year	June	July	August	September	October
1928	572	404	398	249	255
1929	286	348	243	237	152
1930	344	449	435	499	458
1931	940	962	861	820	591
1932	657	542	563	556	394
1933	524	491	637	541	504
1934	667	753	870	933	965
1935	580	630	530	556	487
1936	375	492	482	425	372
1937	336	407	501	508	437
1938	1,296	1,237	1,724	1,263	800

COMMENT

Table 1 indicates the incidence of the reported cases of pertussis for the past ten years, during the months in which this study was conducted. The marked increase in the number of cases in 1938 reached almost epidemic proportions. It was our clinical impression during the investigation that the severity of the disease was correspondingly greater than it had been in previous years. It is apparent that the efficacy of the antigen was subjected to a more rigorous test than would have been the case in any of the preceding nine years.

The age distribution of the treated and that of the untreated patients were practically identical. The majority of our patients were under 4 years of age (table 2). The distribution according to sex is shown in table 3. Most of the children came to the hospital fairly early in the course of the disease. Forty of the 65 children treated and 41 of the 70 children not treated were admitted within the first two weeks after the onset of the disease (table 4). The small number of patients with mild pertussis may be attributed to the fact that such patients usually

do not require hospitalization. However, all of the patients with mild pertussis had classic cough, whoop and emesis during their hospital stay. Almost all of the patients had moderate or severe pertussis, and the

TABLE 2.—*Age of the Treated and Untreated Patients*

Age, Years	Treated	Untreated
0 - ½	4	5
½ - 1	8	8
1 - 2	7	7
2 - 3	13	13
3 - 4	10	13
4 - 5	8	8
5 - 6	7	6
6 - 7	5	6
7 - 8	6	2
8 - 9	2	1
9 -10	0	..
10 -11	0	1

TABLE 3.—*Sex of the Treated and Untreated Patient*

Sex	Treated	Untreated
Male	46	23
Females	19	47

TABLE 4.—*Duration of the Symptoms Before Admission of the Treated Patients and the Controls*

Duration of Symptoms	Treated Patients	Controls
1 week	17	29
2 weeks	23	12
3 weeks	11	12
4 weeks	3	5
Over 4 weeks	3	9
Unknown	8	3

TABLE 5.—*Classification of the Severity of Pertussis on Admission*

Pertussis	Treated Patients	Controls
Mild	7	8
Moderate	34	38
Severe	24	24

numbers of patients in the treated and untreated groups were almost equal (table 5).

The condition of the patients two weeks after admission was compared to their condition on admission in order to determine the presence or absence of clinical improvement. This interval of two weeks was selected in order to allow sufficient time for the antigen to evoke a

therapeutic response. As disclosed in table 6, no significant difference could be noted in the condition of the patients with either mild or severe pertussis who received treatment as compared with those who acted as controls. The antigen did not shorten the course of the disease. In the series of patients with moderate pertussis the results were slightly better in those children who had received the antigen. The response to therapy in the patients having mild pertussis was apparently poor. However, persistence of even an occasional whoop or emesis was sufficient to classify a patient with mild pertussis as unimproved. It is thus apparent that cases of mild pertussis are not suitable for the evaluation of the antigen. The slightly better response among patients having moderate pertussis, as contrasted with the severe, cannot be explained on the basis of dosage. In fact, the doses employed were estimated to be at least four times greater than those recommended for the commercial preparation. Patients having severe pertussis in the treated and in the control group came under our care early enough in the disease for us to expect prompt response to treatment if the antigen was immunologically effective (table 7). We were especially interested

TABLE 6.—*Classification of the Patient's Condition Two Weeks After Admission*

	Treated Patients	Controls
Mild pertussis		
Improved	..	2
Unimproved	7	4
Moderate pertussis		
Improved	20	13
Unimproved	14	27
Severe pertussis		
Improved	8	8
Unimproved	16	16

TABLE 7.—*Relation of Duration of Illness Before Admission to the Response of the Treated and Untreated Patients*

	Mild Pertussis		Moderate Pertussis		Severe Pertussis	
Treated Weeks	Improved	Unimproved	Improved	Unimproved	Improved	Unimproved
1	..	1	5	4	1	6
2	..	3	7	7	2	7
3	..	2	6	2	3	2
4	..	..	2	..	1	1
5	..	..	..	1	1	..
6	..	1	..	..	..	..
Untreated Weeks						
1	..	1	4	13	2	11
2	..	1	3	5	2	1
3	1	1	4	5	1	3
4	..	..	..	2	1	1
5	..	..	1	..	2	..
6	..	..	..	2	..	..
7	1	1	1	..	..	..

in the children under 1 year of age whose condition was severe, since this is the group associated with the greatest frequency of complications and highest mortality. The results in these infants were disappointing (table 8). The doses for some of the later children in this series were increased to the strength used for the older group of children without any noticeable improvement. Administration of the antigen presumably did not prevent the development of bronchopneumonia. Seven children had this complication, and in 5 of these pneumonia developed after their admission. There were 2 deaths from broncho-

TABLE 8.—*Relation of Age to Response in the Treated and Untreated Patients*

	Mild Pertussis, 7 in All		Moderate Pertussis, 34 in All		Severe Pertussis, 24 in All	
Treated Years	Improved	Unimproved	Improved	Unimproved	Improved	Unimproved
0 -½	..	..	..	..	..	2
½ - 1	..	..	1	1	1	2
1 - 2	..	..	4	2	..	1
2 - 3	..	1	4	3	1	4
3 - 4	..	2	2	3	..	2
4 - 5	..	2	1	3	2	..
5 - 6	..	..	2	..	2	3
6 - 7	..	..	2	1	1	2
7 - 8	..	1	3	1	1	..
8 - 9	..	1	1	..	..	..
9 -10	..	..	..	..	..	..

	Mild Pertussis, 8 in All		Moderate Pertussis, 38 in All		Severe Pertussis, 24 in All	
Untreated Years	Improved	Unimproved	Improved	Unimproved	Improved	Unimproved
0 -½	1	1	..	..	..	4
½ - 1	..	..	..	5	..	3
1 - 2	..	..	3	1	1	1
2 - 3	1	1	3	5	1	3
3 - 4	1	1	3	6	2	1
4 - 5	..	2	..	2	1	3
5 - 6	..	..	2	1	3	2
6 - 7	..	..	2	4	..	..
7 - 8	..	..	..	2	..	..
8 - 9	..	..	..	1	..	..
9 -10	..	..	..	..	..	..
10 -11	..	..	..	..	..	1

pneumonia in the total of 135 children, 1 in the treated and 1 in the untreated group. However, the patient in the treated group died three days after having been admitted and received only 1 dose of antigen.

No local or systemic reaction followed the injection of the antigen. There was no exacerbation of cough, whoop and emesis after the administration of the antigen, such as Thompson [9] described in his younger patients. The duration of hospitalization of these children could not be used to indicate the effectiveness of this form of therapy. Many children were kept in the wards for several weeks during their convalescence.

9. Thompson, A. R.: Pertussis Endotoxin in the Treatment of Whooping Cough, Lancet **2**:733, 1937.

SUMMARY AND CONCLUSIONS

The therapeutic efficacy of a detoxified antigen was studied under carefully controlled conditions.

The marked increase in the severity of the disease during the period of observation subjected the antigen to a more rigorous test than would ordinarily be encountered.

Administration of the antigen failed to influence favorably the clinical course of pertussis, especially in the patients with severe pertussis and in the younger groups.

The antigen did not prevent the development of complications of pertussis.

CEREBRAL SCLEROSIS

A. B. BAKER, M.D.
AND
L. S. GERBER, M.B.
MINNEAPOLIS

The subject of cerebral sclerosis is still in a stage of confusion, in spite of numerous attempts to classify the many diseases that fall under this general heading. The countless new names that have been suggested for the various clinical and pathologic variations have not helped to clarify the situation. It therefore seems of advantage to report cases that may facilitate understanding of this not uncommon involvement of the human nervous system. In order for one to appreciate fully the complexity of the subject, a brief summary of the literature is necessary.

Schilder [1] in 1912 described a diffuse disease of the cerebral white substance occurring in childhood. Because of the characteristic macroscopic and microscopic changes, he expressed the belief that this disease constitutes a new entity. His patient was a 14 year old girl who showed failing vision, papilledema, right hemiplegia, aphasia and mental deterioration. Death occurred 5½ months after onset of the illness. Autopsy showed diffuse demyelination of the cerebral hemispheres. The cortex, the arcuate fibers, the basal nuclei and to a certain extent the axis-cylinders were intact. Schilder collected 4 cases which resembled his from the literature (Rossolimo,[2] Ceni,[3] Haberfeld and Spieler [4] and Beneke [5]) and suggested the term "encephalitis periaxialis diffusa" for the disease. He stated that the characteristic pathologic changes in the brain consist of (1) limitation of the disease process to the white matter, with a sharp line of demarcation; (2) destruction of the myelin with apparently secondary and less complete dissolution of the axis-cylinders; (3) wide-

From the Division of Nervous and Mental Diseases and the Department of Pathology of the University of Minnesota.

1. Schilder, P.: Zur Kenntnis der sogenannten diffusen Sklerose (Ueber Encephalitis periaxialis diffusa), Ztschr. f. d. ges. Neurol. u. Psychiat. **10**:1, 1912.

2. Rossolimo, G.: Zur Frage über die multiple Sklerose und Gliose, Deutsche Ztschr. f. Nervenh. **11**:88, 1897.

3. Ceni, C.: Ueber einem interressantem Fall gliomatöser Infiltration beider Grosshirnhemisphären, Arch. f. Psychiat. **31**:809, 1899.

4. Haberfeld, W., and Spieler, F.: Zur diffusen Hirn-Rückenmarksklerose im Kindesalter, Deutsche Ztschr. f. Nervenh. **40**:436, 1910.

5. Beneke: Ein Fall hochgrädigster ausgedehnter Sklerose des Centralnervensystems, Arch. f. Kinderh. **47**:420, 1908.

spread and large accumulations of glial elements and (4) adventitial infiltration of compound granular cells and a variable number of lymphocytes. Schilder expressed the belief that encephalitis periaxialis diffusa is closely related pathogenetically to multiple sclerosis but is not related to pseudosclerosis (described by Westphal[6] in 1883), to tuberous sclerosis or to some forms of diffuse sclerosis of the brain (described grossly by Heubner[7] in 1897).

Since Schilder's report a large number of cases of both diffuse and local demyelination limited to the white matter, with more or less sclerosis, have been recorded in the literature under various descriptive titles. In 1885, Pelizaeus[8] described clinically 5 cases of a familial disease of the brain in which the outstanding symptoms were disturbances of the speech, bradylalia, peculiar facial expressions, ataxia, athetoses, spasticity and mental deterioration. He expressed the belief that the condition in these cases was multiple sclerosis. Merzbacher[9] in 1910 described the pathologic cerebral changes in a patient derived from the same stock as those in the cases described by Pelizaeus. He observed atrophy of the white matter of the entire brain, associated with almost complete degeneration of myelin and axis-cylinders. The cortex and the arcuate fibers were normal. Proliferation of neuroglia cells occurred in the thalamus. Because of the presence of islands of intact nerve fibers and the absence of a uniform glial reaction, Merzbacher expressed the belief that the condition represented a congenital maldevelopment of the white matter and used the descriptive term "Aplasia axialis extracorticalis congenita."

In 1913 Krabbe[10] described perivascular destruction of the white matter with replacement gliosis in a 1 year old child. The cortex was unaffected, and there was no evidence of inflammation. He expressed the opinion that the process had originated perivascularly and that it represented an early stage of diffuse cerebral sclerosis. This condition was described as "perivascular myelin necrosis." Three years later this

6. Westphal, C.: Ueber einem dem Bilde der cerebrospinalen grauen Degenerationähnliche Erkrankung des zentralen Nervensystems ohne anatomischen Befund, nebst einigen Bemerkungen über paradoxe Kontraktion, Arch. f. Psychiat. **14**:87, 1883.

7. Heubner, O.: Ueber diffuse Hirnsklerose, Charité-Ann. **22**:298, 1897.

8. Pelizaeus, F.: Ueber eine eigenthümliche Form spastischer Lähmung mit Cerebralerscheinungen auf hereditärer Grundlage (multiple Sklerose), Arch. f. Psychiat. **16**:698, 1885.

9. Merzbacher, L.: Eine eigenartige familiärhereditäre Erkrankungsform (Aplasia axialis extra-corticalis congenita), Ztschr. f. d. ges. Neurol. u. Psychiat. **3**:1, 1910.

10. Krabbe, K.: Beitrag zur Kenntnis der Frühstadien der diffusen Hirnsklerose (die perivasculäre Marknekrose), Ztschr. f. d. ges. Neurol. u. Psychiat. **20**:108, 1913.

same author,[11] under the title "A New Familial Infantile Form of Diffuse Brain Sclerosis," described 5 more cases, in 4 of which the disease was familial (2 cases in each of two families). He stated that the condition in his cases differed from that in Schilder's in (1) the familial history, (2) its appearance earlier in infancy, (3) its involvement of the entire cerebrum and cerebellum and (4) its degenerative, rather than inflammatory, nature. Krabbe proceeded to classify diffuse cerebral sclerosis of childhood into three groups: diffuse sclerosis of syphilitic origin, encephalitis periaxialis diffusa and a familial infantile form, under which type he included the condition in his cases.

In 1914 Marie and Foix[12] described what they considered a new disease entity as "sclérose intra-cérébrale centrolobaire et symmétrique." They claimed that they were unable to find any case similar to theirs in the literature. Both clinically and pathologically, however, the condition in their case closely resembled that reported by Schilder in 1912.

Jakob[13] in 1915 described a case which he believed presented certain similarities to Schilder's cases but differed in that there was more extensive destruction of the axis-cylinders. Since there were evidences of diffuse inflammation of the white matter, Jakob suggested the term "diffuser infiltrativer Encephalomyelitis." He expressed the belief that this disease was closely related to both diffuse and multiple sclerosis.

The descriptive term "leucoencéphalite subaiguë à foyers successifs" was suggested by Claude and Lhermitte[14] in 1920 to describe a condition similar clinically to Schilder's disease. It was characterized pathologically by demyelination of the white matter, gliosis and infiltration of the perivascular spaces and walls of the blood vessels with lymphocytes. The authors expressed the opinion that the lesions were caused by a toxic infectious process.

In the following year, Hermel[15] used the name "Encephalomyelomalacia chronica diffusa" to describe a case in which the pathologic changes were much like those of Schilder's disease, except that there was complete destruction of the axis-cylinders.

---

11. Krabbe, K.: A New Familial Infantile Form of Diffuse Brain-Sclerosis, Brain **39**:74, 1916.

12. Marie, P., and Foix, C.: Sclérose intra-cérébrale centrolobaire et symétrique: Syndrome paraplégique, Rev. neurol. **22**:1, 1914.

13. Jakob, A.: Zur Pathologie der diffusen infiltrativen Encephalomyelitis in ihre Beziehungen zur diffusen und multiplen Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **27**:290, 1915.

14. Claude, H., and Lhermitte, J.: Leucoencéphalite subaiguë à foyers successifs, Encéphale **1**:89, 1920.

15. Hermel, H.: Ueber einen Fall von Encephalomyelomalacia chronica diffusa bei einem vierjährigen Kinde, Deutsche Ztschr. f. Nervenh. **68**:335, 1921.

In 1923 Spielmeyer [16] studied the pathologic changes in a second case of Pelizaeus-Merzbacher's disease and stated that the disease was not a type of aplasia but that it represented a long-drawn-out process of degeneration. Spielmeyer also noted degenerative changes in the cortex.

The first contributions in English to this subject came from Bouman [17] and from Collier and Greenfield [18] in 1924. Bouman described 2 cases of Schilder's disease and collected 24 others from the literature. He classified these cases into three groups, according to whether the disease process was inflammatory, degenerative or neoplastic. He expressed the belief that the condition was due to a virucidal agent and suggested the term "sclerosing inflammation of the white matter of the brain" as a more descriptive one. Collier and Greenfield's work was similar to Bouman's.

In 1925 Flatau [19] described a case of diffuse sclerosis of the white matter without any signs of inflammation and used the title "encephaloleukopathia scleroticans progressiva." In the same year the occasional familial aspect of diffuse sclerosis in childhood was again emphasized when Scholz [20] reported 5 familial cases, in only 1 of which, however, autopsy was performed. Scholz grouped his cases with those of Krabbe and agreed with the latter in separating them from cases of encephalitis periaxialis diffusa.

Globus and Strauss [21] in 1928 introduced the term "progressive degenerative subcortical encephalopathy," which they thought a more correct title than that of Schilder. They grouped 26 cases, 4 of which were their own, under this title, including the chronic encephalomyelomalacia of Hermel, the perivascular myelin necrosis and the familial infantile form of diffuse cerebral sclerosis of Krabbe, the encephalitis periaxialis diffusa of Schilder, the interlobar symmetric sclerosis of Marie and Foix and the sclerosing encephaloleukopathia of Flatau. Globus and Strauss expressed the belief that the striking limitation of the pathologic process to the white matter singled out these cases from the larger group of diffuse scleroses.

16. Spielmeyer, W.: Der anatomische Befund bei einem zweitem Fall von Pelizaeus-Merzbacher Krankheit, Zentralbl. f. d. ges. Neurol. u. Psychiat. **32**:203, 1923.

17. Bouman, L.: Encephalitis Periaxialis Diffusa, Brain **47**:453, 1924.

18. Collier, J., and Greenfield, J. G.: The Encephalitis Periaxialis Diffusa of Schilder, Brain **47**:489, 1924.

19. Flatau, E.: Encephaloleukopathia scleroticans progressiva, Encéphale **20**:475, 1925.

20. Scholz, W.: Klinische, pathologisch-anatomische, und erbbiologische Untersuchungen bei familiärer, diffuser Hernsklerose im Kindesalter, Ztschr. f. d. ges. Neurol. u. Psychiat. **99**:651, 1925.

21. Globus, J. H., and Strauss, I.: Progressive Degenerative Subcortical Encephalopathy (Schilder's Disease), Arch. Neurol. & Psychiat. **20**:1190 (Dec.) 1928.

Baló [22] in 1928 reported that he had discovered a new disease of the central nervous system, which he termed "encephalitis periaxialis chronica." He used this term to describe a condition in which the cerebral white substance was destroyed in concentric layers, leaving the axis-cylinders practically intact. Most investigators who have surveyed the literature since 1928 have considered the condition in Baló's case to be Schilder's disease.

McKinley [23] in 1931 surveyed the literature and collected 64 cases. He used a simple descriptive classification for the various conditions reported. As a general heading he used the term "diffuse subcortical sclerosis," under which he placed three types: (1) the inflammatory type (under which he included the condition described by Bielschowsky [24]); (2) the hereditary or familial type (Bielschowsky and Henneberg,[25] Scholz,[20] Krabbe [11] and Merzbacher [9]); (3) the primary, essential or nonhereditary type (under which were included those conditions identical with the second type but lacking the hereditary factor).

The work of Ferraro [26] in 1937 is probably the most complete of all papers on this subject. From a study of 4 cases of his own and a complete survey of the literature, he concluded that the fundamental histopathologic processes were substantially the same in the various conditions. He expressed the belief that the clinical manifestations vary from case to case in relation to the age at which onset occurs, the localization of the process, the intensity of the causative factor, the constitutional makeup of the patient and the particular state of resistance at the moment of invasion by the pathogenic agent. He further stated that the familial occurrence of the disease does not constitute sufficient ground for calling it a new entity. Ferraro attempted a classification of primary demyelinating processes in the central nervous system based on both the clinical and the pathologic characteristics of the conditions which he had analyzed.

Besides these many diffuse sclerotic processes, there have been reported many cases in which the cerebral involvement has consisted

---

22. Baló, J.: Encephalitis Periaxialis Concentrica, Arch. Neurol. & Psychiat. **19**:242 (Feb.) 1928.

23. McKinley, J. C.: Diffuse Subcortical Sclerosis of the Brain, Minnesota Med. **14**:162, 1931.

24. Bielschowsky, F.: Die Bedeutung des Infektes für die diffuse Sklerose, zugleich ein Beitrag zur Klinik und Pathologie der diffusen Sklerose, J. f. Psychol. u. Neurol. **33**:12, 1927.

25. Bielschowsky, M., and Henneberg, R.: Ueber familiäre diffuse Sklerose (Leukodystrophia cerebri progressiva hereditaria), J. f. Psychol. u. Neurol. **36**:131, 1928.

26. Ferraro, A.: Primary Demyelinating Processes of the Central Nervous System: An Attempt at Unification and Classification, Arch. Neurol. & Psychiat. **37**:1100 (May) 1937.

of isolated focal lesions. The best known of these focal involvements are "pseudosclerosis" and "progressive lenticular degeneration." The term "pseudosclerosis" was introduced by Westphal [6] in 1883 to describe a chronic disease of the central nervous system characterized by generalized intention tremor, spasticity of the extremities, slowness and weakness of movements, psychic disturbances and slurring speech. No pathologic changes were found to explain the clinical features. The title was used because of the clinical resemblance of the condition to multiple sclerosis. In 1898 and 1899 Strümpell [27] described other cases of pseudosclerosis. In 2 cases the central nervous system was found to be normal on microscopic and macroscopic examination. In the third case there was early cirrhosis of the liver with a practically normal brain. Hösslin and Alzheimer [28] in 1911 summarized the pathologic condition in their case of pseudosclerosis as consisting of a diffusely scattered degenerative lesion of the entire nervous system affecting chiefly the corpus striatum, the thalamus, the subthalamic region and the dentate nucleus. There were no signs of inflammation. The glial cells were mildly increased but showed little tendency to form fibers. Many of the glial cells were "giant cells," some of which were multinuclear. Since that date the term "pseudosclerosis" has been used by German investigators to describe a condition characterized clinically by muscular rigidity, tremor, dysphagia and dysarthria, dementia and in some cases corneal pigmentation. In all such cases cirrhosis of the liver has been found. In certain cases no changes have been found in the nervous system, whereas in others changes similar to those described by Wilson have been observed.

In 1912 Wilson [29] described as "progressive lenticular degeneration" a disease of the motor nervous system which occurs in young persons, is often familial and is characterized by generalized tremor, dysarthria and dysphagia, muscular rigidity and hypertonicity, emaciation, spasmodic contractions and emotionalism. Pathologically, there are two constant characteristics: (1) bilateral symmetric degeneration of the putamen and globus pallidus, especially of the former, and (2) cirrhosis of the liver. Following this report numerous cases of Wilson's disease were recorded. In 1924 Greenfield, Poynton and Walshe [30] collected about 70 cases from the literature. They found that in 30 cases in

27. Strümpell, A.: Ueber de Westphalsche Pseudosklerose und über diffuse Hirnsklerose insbesondere bei Kindern, Deutsche Ztschr. f. Nervenh. **12**:115, 1898.

28. Hösslin, C., and Alzheimer, A.: Ein Beitrag zur Klinik und pathologischen Anatomie der Westphal-Strümpellschen Pseudosklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **8**:183, 1911.

29. Wilson, S. A. K.: Progressive Lenticular Degeneration, Brain **34**:295, 1912.

30. Greenfield, J. G.; Poynton, F. J., and Walshe, F. M. R.: On Progressive Lenticular Degeneration (Hepato-Lenticular Degeneration), Quart. J. Med. **17**: 385, 1924.

which autopsy was performed the lesions described by Wilson were present. They expressed the belief that "pseudosclerosis" and "progressive lenticular degeneration" are the same entity. Hall [31] also expressed a belief in their unity and used the term "hepatolenticular degeneration" to describe both conditions. Barnes and Hurst [32] supported Hall's impressions.

REPORT OF CASES

CASE 1.[33]—C. P., a boy, was born after a difficult labor. An examination shortly after birth revealed the face to be puffy and the eyelids swollen. The pupils were pinpoint and did not react to light. The extremities were rigid and flexed and twitched in spasmodic jerks. The deep reflexes were hyperactive. Any attempt to disturb or examine the child elicited shrill cries.

At first the infant refused to nurse and was fed by gavage. Large doses of calcium and parathyroid extract were administered. After a few months he began to eat well. At 4 months of age the baby was suspected of being blind, and ophthalmoscopic examination revealed bilateral primary atrophy of the optic nerve. An encephalogram which was made shortly afterward demonstrated extensive but symmetric cerebral atrophy, with enlargement of the lateral ventricles. After this procedure the child seemed to improve. The pupils increased in size and for the first time reacted to light.

For a time the infant's condition remained unchanged. At 6 months of age he vomited some dark brown material that gave a positive reaction to the benzidine test for blood. When 10 months of age, with no premonitory signs, he suddenly became limp and pale and died. Throughout life the temperature had been unstable, rising as high as 104 F. without adequate explanation.

Autopsy.—Complete autopsy was performed. There were no significant somatic changes. Removal of the calvarium revealed a great excess of subarachnoid fluid, there being a space of about 2 to 3 cm. between the cortex and inner table of the skull. The brain was small and appeared shrunken, measuring only 10 cm. in its widest portion and 7 cm. in depth. The brain tissue on external examination seemed exceptionally firm and rubbery. Coronal sections were made (fig. 1). These revealed extensive hydrocephalus, the ventricular enlargement apparently resulting from a shrinking or disappearance of the hemispheral white substance. All the white substance was reduced in quantity and in some regions was represented by only a thin core of tissue. The greatest reduction had occurred in the occipital regions, where the white matter measured only 1 mm. in thickness. Along the lateral ventricles there was but 2 mm. of tissue separating the ventricles from the adjoining cortex. The temporal lobes showed the mildest degree of gross involvement. The basal nuclei were firm and pale, and their architecture was almost completely eradicated. In this region there were bilateral symmetric cavities measuring 8 by 10 mm. These cavities were multilocular and were situated almost in the center of the basal nuclei, involving portions of the already altered thalamus, putamen and globus pallidus (fig. 1). The midbrain, pons and medulla were also firm and pale. The pathologic process seemed to extend from the pons along the brachium pontis into the cerebellum, where it replaced the medullary

31. Hall, H. C.: La degenerescence hepato-lenticulaire, Paris, Masson & Cie, 1921.

32. Barnes, S., and Hurst, E. W.: Hepato-Lenticular Degeneration, Brain 48: 279, 1925.

33. This case is reported through the courtesy of Dr. P. Dwan.

core up to the region of the dentate nucleus. The cervical part of the cord was intact. All the involved tissue was extremely firm to palpation and presented a consistency of rubber. The cerebral and the cerebellar cortex appeared normal in every respect. In most regions the cerebral cortex measured 5 mm. in thickness, almost four to five times the thickness of the white substance. The cortex was of a normal color and consistency.

Sections were removed from various areas throughout the brain and stained with the hematoxylin and eosin stain, by the Mallory-Heidenhain technic (azo-carmine), with Weigert's stain for myelin sheath, with the Bielschowsky stain for axis-cylinders, with Holzer's stain for glial fibers, with Mallory's phosphotungstic acid–hematoxylin stain and with Cajal's gold impregnation method.

Microscopic studies revealed the cerebral cortex to be essentially intact. There was no apparent reduction in the number of ganglion cells and no increase in glial elements. The entire pathologic process was strictly limited to the subcortical regions. In all sections of the hemispheral white substance there was a diffuse

Fig. 1 (case 1).—Coronal section through the region of the basal nuclei. The ventricles are enlarged, and the white matter is narrowed. Two symmetric cavities are present in the region of the basal nuclei.

increase in the glial elements. The degree of glial proliferation varied from region to region. It was mild in the temporal lobes, while in the occipital lobes the gliosis was extensive. As a rule the gliosis was diffuse, but in many regions the astrocytic proliferation was patchy, producing many irregular glial nodules interspersed amid the milder diffuse macroglial increase.

With the special stains it was apparent that there was an extensive decrease in the myelin throughout the hemispheres (fig. 2). This decrease was usually diffuse, although its intensity varied greatly from region to region and even varied within the same region. In both the occipital and the parietal lobe many areas showed an almost complete absence of myelin sheaths, while in the temporal lobes many intact sheaths could be observed. Peculiarly enough, no microglial reaction was observed in these regions of diffuse decrease in myelin.

The axis-cylinders showed changes comparable to those of the myelin. In most sections they appeared fragmented and frayed, and in some areas they were entirely absent. In many regions they had lost most of their tinctorial properties and were

barely visible as a faint outline of the original structure. Swellings or irregularities in shape of the axis-cylinders were not observed.

The most interesting alterations were found within the basal nuclei. Here there was also a complete replacement of almost all the tissue by an extensive glial proliferation. This process was more severe here than in any other region of the brain. The glial cells were irregular in outline and had in many cases formed giant cells. Within many of these giant cells there were deposited tiny purple granules which often completely replaced both cellular body and nucleus and even extended outward into the cellular processes, thus providing an excellent picture of the detailed outline of some of these larger astrocytes. In the region of the third ventricle the entire subependymal area was filled with a heavy layer of proliferating astrocytes.

In the center of the basal nuclei, involving part of the thalamus, putamen and globus pallidus, there had occurred a secondary breaking down of the glial tissue with the formation of many large and small cavities. The larger cavities were

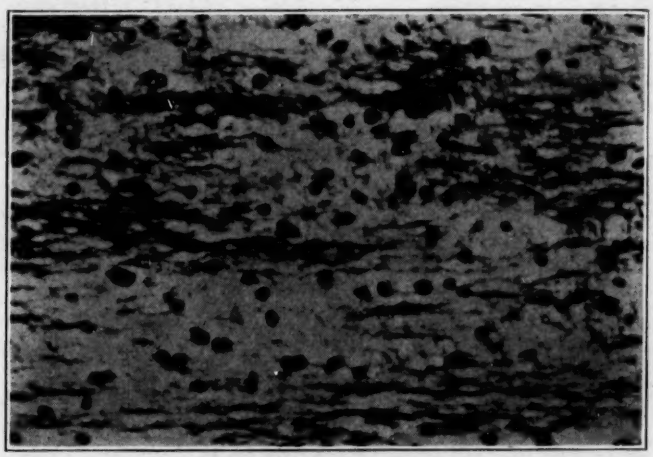

Fig. 2 (case 1).—Section of the white substance from the occipital lobe. With the Weigert stain there is an almost complete absence of myelin in this region.

surrounded by a huge number of fat granule cells in various stages of phagocytosis (fig. 3*A*). Around the wall of these larger cavities there were also observed large bundles of acellular glial fibers which appeared as fragmented structureless masses and which in some areas had extended into the cavities (fig. 3). In the tissue around the larger cavities there appeared all stages of this glial breakdown. These varied from areas in which the tinctorial properties of the tissues had become impaired to regions in which definite fragmentation and vacuolation had resulted, with the formation of scattered clear-staining spaces. In the latter frequently the earliest stages in the microglial reaction could be seen, and many small rod cells as well as small scavengers were visible (fig. 3*B*). No myelin tissue was present within the region of the basal nuclei, and complete destruction of the axis-cylinders had occurred. The nerve cells were almost completely replaced, and only a few distorted cells of the globus pallidus and thalamus were still present.

The pons and medulla showed little involvement, in spite of their apparent firmness to gross palpation. The cells of both structures were intact. The

brachium pontis, however, was replaced by heavy bands of glial fibers extending along the brachium into the cerebellum to the region of the dentate nucleus. A similar replacement of the corpus restiforme had occurred. In both structures there was an almost complete absence of myelin, a fragmentation and loss of tinctorial properties of the axis-cylinders, as well as a diffuse uniform glial replacement. The fourth ventricle showed subependymal gliosis similar to that already described for the third ventricle.

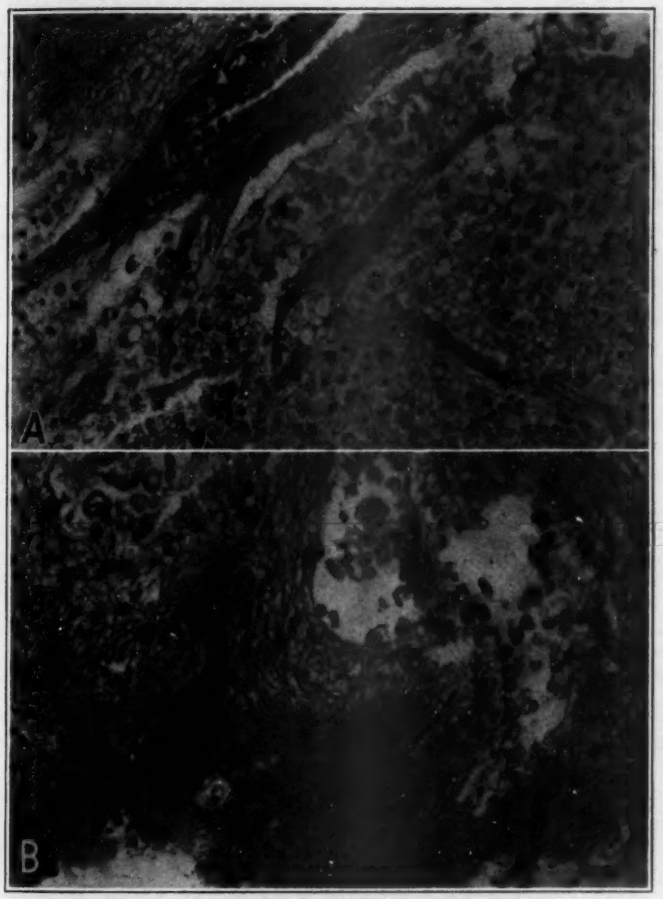

Fig. 3 (case 1).—*A*, a portion of the wall of one of the large cavities in the region of the basal nuclei. Note the large number of fat granule cells in various stages of phagocytosis. Hematoxylin and eosin stain. *B*, a section from the vicinity of the basal nuclei. Note the extensive gliosis and the beginning cavitation. Hematoxylin and eosin stain.

COMMENT

In no region was there any sign of a cellular reaction that could be interpreted as an inflammatory or toxic process. The entire picture seemed to be that of a generalized glial proliferation with a secondary

breakown of the glial tissue in the region of the basal nuclei. It is of interest to note that although the cortex was rigidly spared, the gray masses of the basal nuclei were completely destroyed, thus differentiating this condition from those that are strictly limited to the white substance.

CASE 2.—A 4 year old boy had been cared for in a home for subnormal children for several years. From birth there had never been proper development. He could

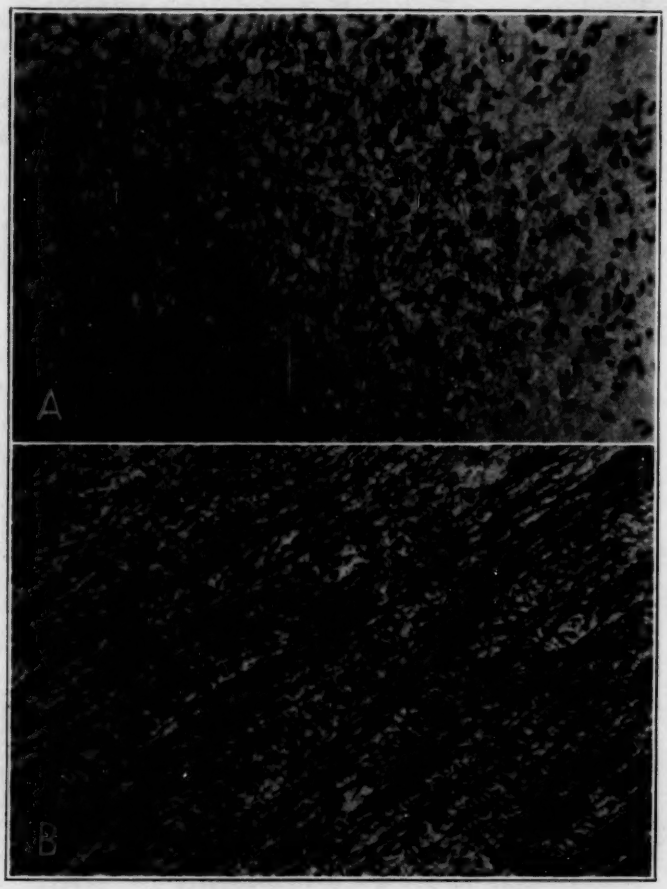

Fig. 4 (case 2).—*A*, actively proliferating astrocytes from the region of the thalamus. Hematoxylin and eosin stain. *B*, partial demyelination as observed with the Weigert stain. This section is from the hypothalamic region.

not talk or feed himself and was always tired and sleepy. His appetite was good, and he was normally active. He could not control the bowels and bladder. He had been getting along fairly well without any complaints until a few days before death, when some bleeding from the left ear occurred. He became unresponsive and would neither stand nor sit up. His condition was not considered serious at this time. He was found dead in his crib.

Autopsy.—Complete autopsy was performed. The child was well nourished and presented a slightly hydrocephalic appearance, the occipitofrontal circumference of the head measuring 53 cm. There were numerous spots of light brown pigmentation scattered over the body as well as many small ulcers of the skin. The general examination revealed nothing abnormal except the brain, which weighed 1,560 Gm. This organ appeared normal externally, but on separation of the hemispheres the thalamus and the head of the caudate nucleus appeared greatly enlarged bilaterally and tended to obliterate the third ventricle. These enlarged structures felt firm to palpation. Coronal sections through the hemispheres showed moderate hydrocephalus and verified the enlargement of the thalamus and caudate nucleus. The thalamus measured 5.5 by 4 cm. and was of a firm, rubbery consistency. This alteration in texture extended inferiorly to involve the hypothalamic region but spared the rest of the basal nuclei. The rest of the hemispheral tissue, the cerebellum and the basal structures were normal.

Sections were removed from numerous regions of the brain, with special attention being placed on the apparently involved regions. These sections were stained in a manner similar to those of case 1.

The entire brain was found normal on microscopic examination with the exception of the thalamic and the hypothalamic region. Here there had occurred definite glial proliferation, which was by far most extensive in the thalamus. Many areas were completely replaced by actively proliferating astrocytes (fig. 4*A*). Where the glial proliferation was extreme a definite replacement of the nerve cells had occurred, although in most regions the nerve cells had been spared. This was especially true in the hypothalamic region, where the astrocytes had proliferated between the groups of nerve cells but had produced no apparent destruction of them. A heavy deposition of glial fibers had not occurred as yet, the replacement being of a more cellular nature.

Myelin destruction was complete in the thalamus but was only mild in the hypothalamic regions (fig. 4*B*). No invasion of the tissue by fat granule cells was observed. No cellular reactions of an inflammatory or toxic nature were seen.

COMMENT

When one considers these 2 cases both clinically and pathologically, one immediately encounters difficulties in attempting to classify them in light of the review of the literature presented. It also becomes apparent why so many different names have been suggested by the various authors to describe the condition in their individual case. Superficially, it seems that the condition in our first case would fit in best with that described by Schilder as encephalitis periaxialis diffusa. Clinically, however, the onset is too early for classic Schilder's disease; also, in our case the gray bodies of the basal nuclei were involved, which is certainly atypical. The early onset in our case as well as the diffuse sclerosis would make it fit nicely in the group of cases described by Krabbe, but in his cases the disease was familial, a factor entirely lacking in our case. Finally, in none of the descriptions presented by the various authors in reports of cases of diffuse sclerosis has there been reported a secondary destruction of the glial elements to produce cavitation of a bilateral symmetric nature. This particular pathologic

characteristic was listed by Wilson as pathognomonic for the lesions that occur in the entity described by him as "progressive lenticular degeneration." In Wilson's disease, however, no diffuse sclerosis was present, and there was always an associated cirrhosis of the liver.

A somewhat similar difficulty in classification is encountered with our second case. Superficially, the lesions of the brain resembled those described by many investigators as pseudosclerosis. In pseudosclerosis, however, there is supposed to be associated hepatic disease, a condition that was entirely lacking in our case.

In view of this difficulty in classification, it seems most practical to list all these cases under the simple title of cerebral sclerosis and then to describe the extent and location of the involvement. Certainly until knowledge of the etiology of the conditions in this large group increases, such an approach would avoid a great deal of the confusion that the coining of new terminology has produced. Moreover, it seems possible that most of these sclerotic processes are definitely interrelated. Certainly our first case, with its bilateral symmetric cavitation associated with diffuse sclerosis, suggests the possibility that even that type of focal sclerosis which includes Wilson's disease and pseudosclerosis is somehow related to the larger group of diffuse scleroses. Aside from the associated damage to the liver, one finds no reason for separating them, and, as our second case demonstrates, focal scleroses may occur without hepatic disease.

SUMMARY

Two cases of cerebral sclerosis are described.

The simple term "cerebral sclerosis" is proposed for that large group of both diffuse and focal sclerotic processes of the brain described in the literature under so many different terms. It is suggested that even Wilson's disease and pseudosclerosis may be related to the more diffuse processes.

A brief review of the literature is presented.

BASAL METABOLISM OF TUBERCULOUS CHILDREN

V. TUBERCULOUS PLEURISY

ANNE TOPPER, M.D.
AND
HAROLD S. RUBIN, M.D.
NEW YORK

During the past five years we have had an unusual opportunity at Sea View Hospital to study the basal metabolism of tuberculous children in almost every phase of the infection. The results of our previous studies may be summarized as follows:

Of 115 children with active afebrile pulmonary tuberculosis of the adult, or reinfection, type, 92, or 80 per cent, had a normal basal metabolic rate (between + 10 and — 10 per cent). The metabolism remained normal even in the presence of extensive pulmonary pathologic change.[1] In this respect, the results agreed in the main with those reported in the literature for adults with the same type of infection.[2]

Studies of the basal metabolism of 66 children in whom pneumothorax had been instituted indicated that the basal metabolism was lowered by this procedure. The longer the pneumothorax was maintained, the lower the metabolic rate seemed to fall. From + 7 per cent before treatment was instituted in this group, the average basal metabolic rate fell to — 3 per cent after six months, to — 5 per cent within a year and to — 10 per cent in those cases in which pneumothorax had been maintained for more than a year.[3]

Of 143 children with active, afebrile tuberculosis of the primary, or childhood, type, only 6, or 4 per cent, had a normal basal metabolic rate. The other 137, or 96 per cent of the entire group, had a basal metabolic rate above + 10 per cent. Many of the children were studied for long periods, ranging from six months to more than three years.

From the Pediatric Service of Dr. Béla Schick, Sea View Hospital, Staten Island, N. Y.

1. Topper, A., and Rosenberg, H.: Basal Metabolism of Tuberculous Children, Am. J. Dis. Child. **52**:266 (Aug.) 1936.

2. McCann, W. S., and Barr, D. P.: Am. Rev. Tuberc. **5**:870, 1922. Barbour, H. G.: Antipyretics: III. Acetylsalicylic Acid and Heat Regulation in Fever Cases, Arch. Int. Med. **24**:624 (Dec.) 1919. Kocher, R. A.: California State J. Med. **19**:430, 1921. Gekler, W. A., and Weigel, B. J.: Southwestern Med. **10**:221, 1926. Frank, L. W., and Safarik, L. R.: Colorado Med. **25**:61, 1928.

3. Topper, A., and Rubin, H. S.: Basal Metabolism of Tuberculous Children: IV. Children with Pneumothorax, Am. J. Dis. Child. **58**:957 (Nov.) 1939.

It was found that these children had increased metabolism as long as there were signs of activity present. When the tuberculous process became inactive, as evidenced by absence of physical signs, by negative roentgenographic observations and by a normal sedimentation rate, the basal metabolism returned to a normal level.[4]

TABLE 1.—*Basal Metabolism of Children with Primary Pulmonary Tuberculosis and Pleurisy with Effusion*

Subject	Sex	Age		Height, Cm.	Sitting Height, Cm.	Weight, Kg.	Erythrocyte Sedimentation Rate, Mm. per Hr.	Pulse Rate	Basal Metabolism, Total Calories per 24 Hr.	Basal Metabolic Rate, %*	Comment
		Years	Months								
1	♀	9	7	128	69	29	..	96	1,101	+16	Primary tuberculosis; effusion
		10	2	132	73	38	6	84	1,165	+ 9	Clinically normal
2	♂	14	3	152	80	51	..	100	1,543	+21	Primary tuberculosis; effusion
		14	9	153	81	52	..	88	1,443	+10	Clinically normal
3	♂	8	..	108	58	18	..	104	858	+26	Primary tuberculosis; effusion
4	♂	8	10	117	61	23	31	104	988	+32	Primary tuberculosis; effusion
5	♀	9	..	127	68	20	23	96	1,080	+17	Primary tuberculosis; effusion
6	♂	12	4	138	74	49	32	92	1,320	+21	Primary tuberculosis; effusion
7	♂	14	8	152	75	35	33	82	1,056	— 6	Calcification, primary complex; effusion
8	♂	10	1	133	68	27	35	108	1,222	+32	Primary tuberculosis; effusion
		10	9	137	71	38	29	100	1,481	+40	Primary tuberculosis; effusion
		11	9	148	77	43	4	82	1,339	+13	Clinically normal
9	♂	10	6	135	72	32	..	90	1,196	+16	Primary tuberculosis; effusion
10	♂	7	7	118	66	24	37	98	1,130	+30	Primary tuberculosis; effusion
		8	7	125	69	28	25	92	1,119	+17	Clearing
		9	..	127	70	29	12	80	1,036	+ 6	Clinically normal
11	♀	5	..	112	61	28	54	104	1,104	+33	Primary tuberculosis; effusion
12	♂	7	11	125	68	21	34	100	1,181	+27	Primary tuberculosis; effusion
		8	5	128	69	25	13	72	950	— 1	Clinically normal
13	♀	14	10	152	79	54	38	100	1,542	+24	Primary tuberculosis; effusion
		15	6	154	81	57	19	80	1,464	+11	Clinically normal
14	♀	8	..	127	67	31	19	86	929	+ 4	Calcification, primary complex; effusion
15	♂	6	..	118	64	24	35	100	954	+17	Primary tuberculosis; effusion
16	♀	8	6	130	66	27	34	100	1,065	+22	Primary tuberculosis; effusion
		9	5	137	73	30	16	84	1,090	+ 2	Clinically normal
17	♀	7	2	126	67	25	43	99	1,052	+17	Primary tuberculosis; effusion
		8	2	134	73	34	9	80	1,060	— 2	Clinically normal
18	♂	8	4	118	63	22	46	106	977	+23	Primary tuberculosis; effusion
		9	3	127	66	25	31	92	1,201	+24	Primary tuberculosis; effusion
		10	..	130	68	30	38	98	1,166	+26	Primary tuberculosis; effusion
		14	..	150	80	40	10	74	1,350	+ 6	Clinically normal
19	♂	7	..	123	64	24	52	106	1,138	+39	Primary tuberculosis; effusion
20	♂	9	6	135	70	31	36	100	1,194	+22	Primary tuberculosis; effusion
		10	..	137	70	32	4	80	1,025	+ 5	Clinically normal
21	♂	13	8	151	80	41	24	102	1,673	+30	Primary tuberculosis; effusion
22	♂	5	..	113	61	20	50	120	1,141	+53	Primary tuberculosis; effusion
23	♀	8	5	118	65	32	45	104	1,100	+30	Primary tuberculosis; effusion
		9	..	122	68	33	12	84	1,006	+ 8	Calcification, primary complex; small effusion
24	♂	10	9	134	74	37	10	76	1,183	+ 8	Calcification, primary complex; small effusion

* The standard used was that of Pirquet ("An Outline of the Pirquet System of Nutrition," Philadelphia, W. B. Saunders Company, 1922).

4. Topper, A., and Shore, J.: Basal Metabolism of Tuberculous Children: II. Afebrile Primary Pulmonary Tuberculosis, Am. J. Dis. Child. **58**:119 (July) 1939.

TABLE 2.—*Basal Metabolism of Children with Primary Intrathoracic Tuberculosis and Pleurisy with Effusion*

Subject	Sex	Age		Height, Cm.	Sitting Height, Cm.	Weight, Kg.	Erythrocyte Sedimentation Rate, Mm. per Hr.	Pulse Rate	Basal Metabolism, Total Calories per 24 Hr.	Basal Metabolic Rate, %*	Comment
		Years	Months								
1	♂	10	..	140	75	28	56	100	1,562	+38	Enlarged hilar nodes; effusion
2	♂	7	..	124	65	25	14	108	1,123	+14	Enlarged hilar nodes; effusion
3	♀	15	..	154	83	52	30	100	1,629	+18	Hilar glands; effusion
4	♀	7	5	114	62	21	45	99	972	+26	Paratracheal glands; effusion
		8	5	118	65	32	..	104	1,100	+30	Paratracheal glands; effusion
5	♂	7	6	119	63	21	19	98	937	+18	Hilar glands; effusion
		8	..	123	65	21	17	96	990	+17	Hilar glands; effusion
		8	5	124	66	25	..	90	1,020	+17	Hilar glands; effusion
6	♂	6	..	113	60	22	43	100	1,092	+50	Paratracheal glands; effusion
7	♀	13	..	150	79	35	60	106	1,490	+20	Hilar nodes; effusion
8	♂	13	..	142	74	40	38	104	1,339	+23	Hilar glands; effusion
9	♂	8	3	128	66	23	24	102	1,060	+22	Hilar nodes; effusion
10	♂	11	9	145	79	48	36	102	1,536	+23	Hilar nodes; effusion
11	♂	12	9	141	71	34	35	108	1,224	+21	Hilar nodes; effusion
12	♀	5	4	100	57	17	49	108	864	+28	Hilar nodes; effusion
		5	10	100	58	20	56	110	886	+27	Hilar nodes; effusion
13	♀	6	..	117	62	22	18	94	883	+15	Hilar glands; small effusion
14	♀	12	6	152	77	51	36	92	1,413	+19	Tracheobronchial glands; effusion
15	♀	11	..	148	78	49	28	99	1,468	+21	Hilar nodes; small effusion
16	♂	9	..	133	70	34	32	98	1,128	+15	Hilar glands; effusion

TABLE 3.—*Basal Metabolism of Children with Adult (Reinfection) Type of Pulmonary Tuberculosis and Pleurisy with Effusion*

Subject	Sex	Age		Height, Cm.	Sitting Height, Cm.	Weight, Kg.	Erythrocyte Sedimentation Rate, Mm. per Hr.	Pulse Rate	Basal Metabolism, Total Calories per 24 Hr.	Basal Metabolic Rate, %*	Comment
		Years	Months								
1	♂	15	..	161	84	64	32	68	1,536	— 1	Active tuberculosis; effusion
2	♂	14	..	154	83	48	25	88	1,278	— 9	Active tuberculosis; effusion
3	♂	14	..	144	74	36	42	84	1,164	+ 6	Active tuberculosis; no effusion
		15	..	152	80	38	42	68	1,274	— 2	Active tuberculosis; tuberculous empyema
4	♂	15	..	158	77	35	21	84	1,092	— 7	Active tuberculosis; effusion
5	♀	13	..	155	80	38	19	92	1,210	— 5	Active tuberculosis; effusion
6	♀	13	..	160	85	67	27	105	1,617	+12	Active tuberculosis; small amount of fluid
7	♀	10	..	129	70	30	44	80	980	+ 1	Extensive tuberculosis; effusion
8	♀	12	3	143	76	28	34	100	1,287	+11	Active tuberculosis; effusion; peritonitis
9	♀	13	7	152	77	38	14	96	1,205	+ 2	Active tuberculosis; effusion
		14	3	153	80	48	4	72	1,318	+ 3	Active tuberculosis; effusion resolved
10	♂	10	4	134	73	33	20	98	1,269	+20	Active tuberculosis; effusion
11	♂	10	6	135	72	32	..	88	1,176	+14	Active tuberculosis; effusion
12	♀	14	..	151	82	53	..	96	1,542	+15	Active tuberculosis; effusion
13	♀	13	5	148	77	35	7	98	1,305	+10	Active tuberculosis; effusion
14	♂	9	..	127	65	24	..	120	973	+15	Active tuberculosis; effusion
15	♀	11	..	142	73	37	4	84	1,102	+ 3	Active tuberculosis; effusion

TABLE 4.—*Basal Metabolism of Children with Pleural Effusion Without Pulmonary or Intrathoracic Involvement*

Subject	Sex	Age		Height, Cm.	Sitting Height, Cm.	Weight, Kg.	Erythrocyte Sedimentation Rate, Mm. per Hr.	Pulse Rate	Basal Metabolism, Total Calories per 24 Hr.	Basal Metabolic Rate, %	Comment
		Years	Months								
1	♀	14	..	154	81	45	..	80	1,296	— 1	Effusion; positive Mantoux reaction
2	♂	14	..	145	78	35	15	90	1,272	+ 5	Effusion; positive Mantoux reaction
3	♀	8	9	132	70	27	..	80	950	— 3	Effusion; positive Mantoux reaction
4	♀	13	..	158	83	50	62	92	1,421	+ 3	Effusion; positive Mantoux reaction
5	♂	9	6	142	77	32	31	108	1,336	+13	Effusion; positive Mantoux reaction

TABLE 5.—*Basal Metabolism of Children with Thickened Pleura*

Subject	Sex	Age		Height, Cm.	Sitting Height, Cm.	Weight, Kg.	Erythrocyte Sedimentation Rate, Mm. per Hr.	Pulse Rate	Basal Metabolism, Total Calories per 24 Hr.	Basal Metabolic Rate, %	Comment
		Years	Months								
1	♂	13	5	152	81	44	9	84	1,334	+ 3	Clinically normal
2	♀	12	4	153	78	41	7	82	1,239	+ 2	Clinically normal
3	♂	12	8	139	74	52	32	100	1,342	+23	Active primary tuberculosis
4	♀	11	7	148	78	40	10	86	1,350	+10	Clinically normal
5	♀	10	..	131	71	31	20	90	1,032	+ 5	Clinically normal
6	♀	15	..	151	80	47	29	72	1,234	— 4	Active adult tuberculosis
7	♀	15	..	152	80	54	34	98	1,234	— 1	Active adult tuberculosis
8	♀	9	..	132	70	27	12	78	950	— 3	Clinically normal
9	♀	10	2	132	73	38	6	84	1,165	+ 9	Clinically normal
10	♂	14	9	153	81	52	9	88	1,443	+10	Clinically normal

In a group of 50 children with tuberculosis of the bones, 36 had normal metabolism, irrespective of whether the lesion was frankly active or apparently inactive. Of the 14 children with an elevated basal metabolic rate, 12 had an active primary lesion. Tuberculous infection of bone tissue per se evidently did not affect the metabolism.[5]

The purpose of this paper is to present the results of studies of the metabolism of children with tuberculous pleurisy.

Seventy children, ranging in age from 5 years to 15½ years, were studied. There were 33 girls and 37 boys. Although we realize that the metabolism of boys is consistently and perceptibly higher than that of girls,[6] we did not make a differentiation on the basis of sex for the

5. Topper, A.: Basal Metabolism of Tuberculous Children: III. Tuberculosis of Bone, Am. J. Dis. Child. **58**:768 (Oct.) 1939.

6. Benedict, F. G., and Talbot, F. B.: Metabolism and Growth from Birth to Puberty, Publication 302, Carnegie Institution of Washington, 1921, p. 176.

purpose of this study. However, since we know that tuberculosis of the pleura may be associated with primary intrathoracic or primary pulmonary tuberculosis or may be part of the reinfection phase of pulmonary tuberculosis, we deemed it advisable to make a differentiation on the basis of the underlying pathologic conditions. On this basis, the children were divided into five groups: (1) 24 children with active primary pulmonary tuberculosis and pleurisy with effusion; (2) 16 children with active primary intrathoracic tuberculosis and pleurisy with effusion; (3) 15 children with active adult pulmonary tuberculosis and pleurisy with effusion; (4) 5 children with pleural effusion in whom no evidence of parenchymal or intrathoracic involvement could be found on roentgen examination, and (5) 10 children with thickened pleura.

All the children had normal temperatures at the time of study. Since tuberculosis is a chronic disease in which there may be long periods of apyrexia associated with active infection, it was possible to study the metabolism uninfluenced by an increase in body temperature.

OBSERVATIONS

Of the 24 children in the first group (table 1), all but 3 (subjects 7, 14 and 24) had an increased basal metabolic rate which ranged from + 16 to + 53 per cent, or an average of + 26 per cent for the group. All these children had active primary tuberculosis, evidenced by physical and roentgenographic signs, and an increased erythrocyte sedimentation rate. The basal metabolism of patients restudied when the infection was presumably inactive (subjects 1, 2, 8, 10, 12, 13, 16, 17, 18, 20 and 23) was found to be normal. Subjects 7, 14 and 24, whose metabolism was normal, were also clinically normal at the time of study, the only sign of activity of the tuberculous infection being the pleural effusion.

The basal metabolic rate of the 16 children of the second group (table 2) ranged from + 14 to + 50 per cent, the average being +23 per cent. Although no parenchymal change was evident in this group, all the children had active primary tuberculosis with involvement of hilar, paratracheal or tracheobronchial glands.

The results obtained for these two groups again emphasized the fact that active primary tuberculosis is associated with an increase in the basal metabolism. Pleural effusion per se evidently does not affect the metabolism.

For the 15 children in the third group (table 3), except for subject 10, whose metabolic rate of + 20 per cent remains unexplained, the metabolic rate ranged from — 9 to + 15 per cent, with an average of + 8.6 per cent. All these children had active tuberculosis of the adult type. Many of them had extensive pulmonary involvement; yet, as with the large group of children with adult tuberculosis whose cases

we have previously reported, their metabolism remained normal. The pleural reaction evidently did not affect the metabolism.

There were 5 children (table 4) in whom pleural effusion was the only sign of active tuberculosis present. Since all these children reacted positively to tuberculin and were in an institution for tuberculous patients, they evidently at some time or another had had active tuberculosis. At the time of study, however, the only sign of activity was the effusion. This reaction did not seem to influence the metabolism, since the range of the rates in this group was from —3 to +13 per cent, with an average of +3.4 per cent.

Although the 10 children in the fifth group (table 5) did not have any effusion, thickened pleura was present. They are included in this series merely for completeness of record. One child in this group (subject 3) had evidence of active primary tuberculosis, with a metabolic rate of +23 per cent. Two children (subjects 6 and 7) had active adult tuberculosis, while the remaining 7 were clinically normal. These 9 children had normal metabolic rates ranging from —3 to +10 per cent, with an average of +3 per cent. Evidently the chronic inflammatory process with production of new connective tissue which results in thickening of the pleura is accomplished without affecting the metabolism.

COMMENT

These studies indicate that tuberculous pleurisy, whether in the stage of effusion or of thickening, does not affect the basal metabolism. The fact is again emphasized, however, that active primary tuberculosis is associated with increased basal metabolism.

From our extensive studies of the metabolism of tuberculous children we have found that the only type of tuberculosis that seems to influence the metabolism is the active primary type. So consistently, in fact, does increased basal metabolism reflect activity of a primary infection that we believe we have found in the basal metabolic rate an additional criterion of activity of this type of lesion. Today, at Sea View Hospital, before a child's tuberculosis is declared inactive and he is considered ready for discharge, not only must there be absence of physical and clinical signs and of roentgenographic evidence of tuberculosis and a normal sedimentation rate, but he must have a normal basal metabolic rate.

Although the reason for the increased metabolism in primary tuberculosis has not as yet been absolutely established, we believe that it must be related to pathologic and immunologic differences inherent in this type of infection. The primary infection shows a predilection for lymphatic tissue. There is a general reaction, with intensive reactivity

of the lymphatic system.[7] As previously pointed out, lymphatic tissue has a high metabolic activity, normally ranging between that of embryonic tissue and that of tumor tissue.[8] With increased functional activity, the metabolic activity of lymph tissue increases tremendously, resulting in increased oxygen consumption, which in turn is reflected in increased basal metabolism.

SUMMARY AND CONCLUSIONS

Studies were made on the basal metabolism of 70 children with tuberculous pleurisy. Forty of them had active primary tuberculosis associated with tuberculous effusion. The majority of these children had an increased basal metabolic rate, ranging from + 14 to + 53 per cent, an average of + 25 per cent. The metabolism in many of these patients restudied at a time when the infection was inactive was found to be normal.

There were 15 children in whom the pleurisy was part of the adult, or reinfection, type of tuberculosis. The metabolic rates of these children were normal, averaging + 8.6 per cent.

Pleural effusion per se without demonstrable parenchymal or glandular involvement was without effect on the basal metabolism.

Pleural reaction in the form of thickening of the pleura did not influence the basal metabolism.

These studies emphasize our conclusions from previous studies; namely, that active tuberculosis of the primary type is usually associated with increased heat production.

The reasons for the increased heat production peculiar to this type of tuberculosis alone have been briefly discussed.

7. Schick, B.: M. Clin. North America **12**:561, 1928.

8. Warburg, O.: The Metabolism of Tumours: Investigations from the Kaiser Wilhelm Institute for Biology, Berlin—Dahlem, translated by F. Dickens, London, Constable & Co., Ltd., 1930.

DEXTROSE TOLERANCE TESTS OF THE NEWBORN

ROSE C. KETTERINGHAM, B.S.
CLEVELAND

The present study was undertaken to answer the following questions: Does the dextrose tolerance curve of the infant of a diabetic mother show abnormality? How does it compare with the reaction of the infant of a normal mother to the same test? While this study does not provide complete answers, it does bring out certain interesting tendencies.

A summary of previous observations reported from this laboratory shows that blood sugar values three to six hours after birth ranged from 55 to 80 mg. per hundred cubic centimeters, the mean of ten determinations being 66.8 mg.[1] Seven infants of mothers who received 500 cc. of a 10 per cent solution of dextrose intravenously during the second stage of labor presented blood sugar values of 45 to 65 mg. two hours after birth, with a slight rise to between 55 and 80 mg. four hours after birth.[2] During the first three days of life values determined three and a half to four hours after feeding showed that a gradual rise occurs in both range and mean, as may be seen in the frequency distribution in table 1.[1]

To the previously reported data I now add blood sugar values obtained for babies 5 to 10 days old three and a half to four hours after feedings. Determinations for 16 normal newborn infants ranged from 70 to 95 mg. per hundred cubic centimeters, with a mean of 81.2 mg. It seems, therefore, that the trend noted during the first three days of life coincides with the establishment of feeding and that the plateau of the distribution becomes apparent toward the end of the first week. Single determinations showed no significant difference between the blood sugar of breast-fed and that of formula-fed infants. The effect of feeding was not investigated in greater detail, since the custom of giving supplementary feedings to breast-fed babies makes possible only an

From the Laboratory of the Maternity Hospital.

1. Ketteringham, R. C., and Austin, B. R.: Blood Sugar During Labor, at Delivery and Postpartum, with Observations on Newborns, Am. J. M. Sc. **195**:318 (March) 1938.

2. Ketteringham, R. C., and Austin, B. R.: Induced Hyperglycemia at Delivery —Its Effect and Application, Am. J. Obst. & Gynec. **37**:1000 (June) 1939.

approximate classification. Brown,[3] who investigated the blood sugar of normal and of undernourished infants, found distinctly lower values when the infants were under 2 weeks of age than after this time. Lucas and his associates,[4] in a study of the blood chemistry of breast-fed infants, reported venous blood sugar values ranging from 45 to 80 mg. per hundred cubic centimeters during the first three days of life, with a gradual increase until the tenth day, when a plateau was reached. Greenwald and Pennell,[5] in a large series of determinations of the blood sugar of breast-fed infants, found an average of 76 mg. with capillary blood and a range of 60 to 100 mg., with an increase during the first few days of life to a similar plateau. The practice of supplementary feedings has probably brought about a slight acceleration in the attainment of this plateau, but when the analytic methods are considered the figures presented here parallel those reported by others.

TABLE 1.—*Frequency Distribution of Blood Sugar Values for the Newborn*

Blood Sugar Value, Mg. per 100 Cc.	First Day	Second Day	Third Day	Fifth to Tenth Day
45-54.9	2	1	0	0
55-64.9	16	10	5	0
65-74.9	17	21	14	1
75-84.9	7	8	20	10
85-94.9	2	0	2	5
Over 95	1	1	1	0
Range (mg. per 100 cc.)	55-75	55-75	65-85	70-95
Mean (mg. per 100 cc.)	68.8	70.8	75.1	81.2

METHOD OF TESTING

Since no standard technic for testing the dextrose tolerance of newborn infants has been widely used, the following procedure was adopted for this work. The initial blood sugar determination was made three and a half to four hours after feedings. Dextrose (1.75 Gm. per kilogram of body weight, as a 10 per cent solution) was then administered orally as a substitute for breast milk or formula, and observations were continued until the next feeding was due. Determinations of blood sugar were made one-half, one, two, three and four hours after the midpoint of the period necessary for ingestion.

3. Brown, M. J.: Sugar Content of the Blood in Normal and Undernourished Children, and the Effect of Fat on Absorption of Carbohydrate, Quart. J. Med. **18**:175 (Jan.) 1925.

4. Lucas, W. P.; Dearing, B. J.; Hoobler, H. R.; Cox, A.; Jones, M. R., and Smythe, F. S.: Blood Studies in the Newborn: Morphological; Chemical; Coagulation; Urobilin and Bilirubin, Am. J. Dis. Child. **22**:525 (Dec.) 1921.

5. Greenwald, H. M., and Pennell, S.: The Carbohydrate Metabolism of the Normal New-Born Infant: I. Average Concentration of the Blood Sugar, Am. J. Dis. Child. **39**:281 (Feb.) 1930.

As in the previous work at this laboratory, the Jeghers-Myers modification [6] of the Folin-Malmros [7] ferricyanide micromethod was used for blood sugar determinations. Blood was easily obtained from the heel by puncturing it with a Bard-Parker no. 11 blade. Sufficient filtrate was obtained from 50 cu. mm. of blood to yield duplicate readings, practically all of which checked within 3 per cent. Colorimetric readings were made through a trinitrophenol filter against standards equivalent to 70, 105, 140 and 175 mg. per hundred cubic centimeters of dextrose. Although I have been unable to find any other reports on blood sugar values of the newborn determined by this method, in my hands it has yielded satisfactory results.

The oral dosage of dextrose sufficient to provoke a maximal rise has apparently not been determined for infants, but supposedly they can utilize relatively larger amounts of carbohydrates than can adults. Brown [8] made dextrose tolerance tests on 10 normal infants from 7 weeks to 13 months of age, using 1 Gm. of carbohydrate per kilogram of body weight, dissolved in water sufficient to make a feeding for a child of the age tested. Spence [8] tested 7 infants less than 8 months of age, including an infant 6 days old, by incorporating various carbohydrates in milk. Tisdall, Drake and Brown [9] studied the blood sugar of infants from 1 month to 18 months of age after the ingestion of 1 ounce (solid or liquid not specified) of various carbohydrates, but no conclusions were reported because of the variability in the results. MacLean and Sullivan [10] determined the dextrose tolerance of numerous normal infants from 5 weeks to 3 years of age, using 1.75 Gm. of dextrose per kilogram of body weight, as a 50 per cent solution, with not less than 10 Gm. for infants; by this procedure, a baby of 5 weeks who weighed only 2,825 Gm. received an excess of 3.5 Gm. per kilogram. Rector and Jennings [11] made dextrose tolerance tests on a number of children having signs of hypoglycemia, the youngest being 27 months of

6. Jeghers, H. J., and Myers, V. C.: A Reduction in the Amount of Blood Required for the Folin Micro Blood-Sugar Method, J. Lab. & Clin. Med. **15**:982 (July) 1930.

7. Folin, O., and Malmros, H.: An Improved Form of Folin's Micro Method for Blood Sugar Determinations, J. Biol. Chem. **83**:115 (July) 1929.

8. Spence, J. C.: Some Observations on Sugar Tolerance, with Special Reference to Variations Found at Different Ages, Quart. J. Med. **14**:314 (July) 1921.

9. Tisdall, F. F.; Drake, R. G. H., and Brown, A.: Studies on the Carbohydrate Metabolism of Infants, J. Lab. & Clin. Med. **10**:1 (June) 1925; The Carbohydrate Metabolism of the Normal Infant, Am. J. Dis. Child. **30**:675 (Nov.) 1925.

10. MacLean, A. B., and Sullivan, R. C.: Dextrose Tolerance in Infants and Young Children, Am. J. Dis. Child. **37**:1146 (June) 1929.

11. Rector, J. M., and Jennings, R. E.: Functional Hypoglycemia of Childhood, with Particular Reference to Recurrent Convulsive Manifestations, Am. J. Dis. Child. **53**:1012 (April) 1937.

age. They also used 1.75 Gm. per-kilogram of body weight. Cooperstock and Galloway,[12] in modifying the one hour, two dose dextrose tolerance test of Exton and Rose [13] for infants and children, gave 1.75 Gm. per kilogram of body weight as a 15 to 20 per cent solution divided into two equal doses, except to infants of less than 7 Kg., to whom two doses of 5 Gm. were given. Ten of their 30 normal controls were from 1 month to 2 years of age; the only significant condition observed with regard to this age group was the smaller average rise at thirty minutes. Greenwald and Pennell [14] studied the effect of the ingestion of 2 Gm. per kilogram of various carbohydrates in newborn infants, determining the blood sugar one-half, one and two hours after the feeding of a 20 per cent solution. They felt that the curves obtained with dextrose were definitely lower than those obtained for adults by a similar technic; the average blood sugar at one-half hour was 112 mg. per hundred cubic centimeters and at one hour, 115 mg., and the blood sugar of the infant showing the highest value was around 150 mg. Capillary blood was used for all these studies except by MacLean and Sullivan.

In testing newborn infants there is no logical reason for abandoning the principle of dosage based on body weight. A common, if arbitrary, dose for older infants seems to be 1.75 Gm. per kilogram, so this amount was selected for use in this study. As a 10 per cent solution it is quickly absorbed [15] and readily available already sterilized, and the dosage when computed was found to be an amount of fluid equal to the size of the feeding generally taken by the infant under observation.

Fifteen normal newborn infants who had begun to regain the weight lost after delivery were used as a control group. Nine girls and 6 boys between 5 and 10 days of age were tested. Nine were breast fed, or almost entirely so, and 6 were fed by formula; 8 were white and 7 Negro. Weights ranged from 2.6 to 3.6 Kg. at the time of testing.

With one exception I fed all the controls, as it was noted that a slightly different technic of feeding tended to vary the time of ingestion. Practically all the controls took the dextrose offered within five minutes. No regurgitation was experienced when the baby eructated properly after feeding.

---

12. Cooperstock, M., and Galloway, J. M.: One Hour, Two Dose Dextrose Tolerance Test, Am. J. Dis. Child. **55**:1221 (June) 1938.

13. Exton, W. G., and Rose, A. R.: The One-Hour Two-Dose Dextrose Tolerance Test, Am. J. Clin. Path. **4**:381 (Sept.) 1934.

14. Greenwald, H. M., and Pennell, S.: The Carbohydrate Metabolism of the Normal New-Born Infant: II. The Effect on the Concentration of the Blood Sugar of Feeding Various Sugars to New-Born Infants, Am. J. Dis. Child. **39**:493 (March) 1930.

15. Beeler, C.; Bryant, A. W.; Cathcart, E. P., and Fitz, R.: Improved Alimentary Glucose Tolerance Test, J. Metab. Research **1**:549 (April) 1922.

Specimens of urine were obtained during the first half of the test period from all controls. All specimens were negative for reducing substances.

RESULTS

Table 2 gives the blood sugar values for 15 normal infants tested by the method described here. In all infants the blood sugar showed a rise, but in none was the maximum so high that it could be considered abnormal. The comparatively longer period of observation brings out clearly the postalimentary, hypoglycemic reaction of Foster[16]; 11 of the 14 babies studied showed this. Ten of the 15 controls reached fasting range after two hours, and the remainder reached it within three hours.

TABLE 2.—*Data on the Dextrose Tolerance of Normal Newborn Infants*

Age, Days	Race	Sex	Weight, Kg.	Blood Sugar Value, Mg. per 100 Cc.					
				Start	½ Hour	1 Hour	2 Hours	3 Hours	4 Hours
				Group 1. Formula-Fed Infants					
6	N	♀	2.70	88.6	160.2	148.0	129.8	71.4	....
8	W	♀	3.49	80.0	134.0	114.2	79.7	81.7	90.3
8	W	♀	3.14	70.4	110.6	129.3	75.3	70.0	74.5
6	N	♂	3.13	88.2	144.9	134.2	85.2	79.2	88.0
9	W	♀	3.05	68.0	135.2	120.5	70.0	67.8	72.0
6	N	♂	2.99	90.3	174.1	167.6	111.2	72.2	78.0
				Group 2. Breast-Fed Infants					
8	W	♂	3.00	87.2	166.0	181.8	84.4	71.2	74.5
8	W	♀	3.61	84.9	119.0	129.5	146.6*	79.9	77.0
10	W	♀	3.18	75.3	121.3	130.2	120.9	84.9	77.8
8	W	♀	3.44	86.7	133.5	141.4	110.9	86.5	91.4
6	N	♂	3.36	83.5	140.3	137.6	87.2	72.2	75.7
6	N	♀	2.67	82.8	128.9	132.9	81.1	74.5	67.3
5	N	♂	2.98	75.9	134.0	154.7	92.4	63.2	67.6
7	W	♀	2.76	....	143.2	127.3	80.2	78.1	83.1
5	N	♂	2.60	77.4	136.8	148.1	89.5	76.8	81.7
Mean				81.4	138.8	139.8	96.3	75.3	80.7

* Omitted in chart 2.

Analysis of the data shows that two types of curve exist; in the first the maximum blood sugar value is reached one-half hour after the midpoint of the period necessary for ingestion of the dextrose, while in the second the maximum is delayed until one hour afterward. Since the mean values for the fifteen curves obtained in this study cancel this classification, table 2 has been subdivided on the basis of the configuration of the curve. These two types of curve are independent of age, color, sex or weight. The only factor with which they can be correlated is feedings. In formula-fed infants the maximum blood sugar level was reached within one-half hour, while in the breast-fed babies the

16. Foster, G. L.: Studies on Carbohydrate Metabolism: II. An Interpretation of the Blood Sugar Phenomena Following Ingestion of Glucose, J. Biol. Chem. **55**:303 (Feb.) 1923.

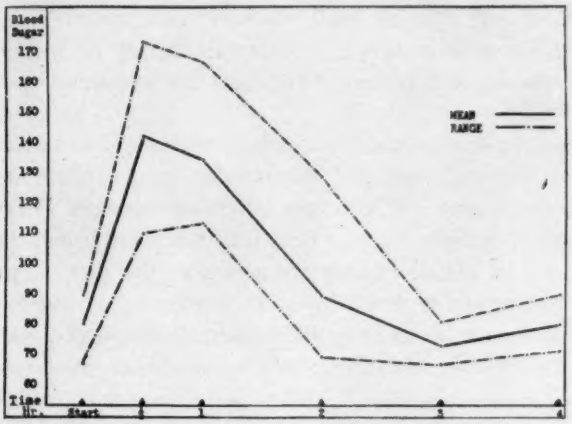

Chart 1.—The range and mean of the blood sugar values for 6 formula-fed infants. The mean fasting blood sugar level is 80.9 mg. per hundred cubic centimeters, and the mean maximum is 143.2 mg., a mean maximum rise of 62.3 mg. Five of the six curves follow the configuration of the mean curve; i. e., the maximum blood sugar concentration is reached at one-half hour, with a slight fall at one hour. The formula-fed infant who did not present this type of curve showed a high tolerance for carbohydrates, a maximum of only 129 mg. being reached. All of the infants showed the hypoglycemic reaction of Foster.

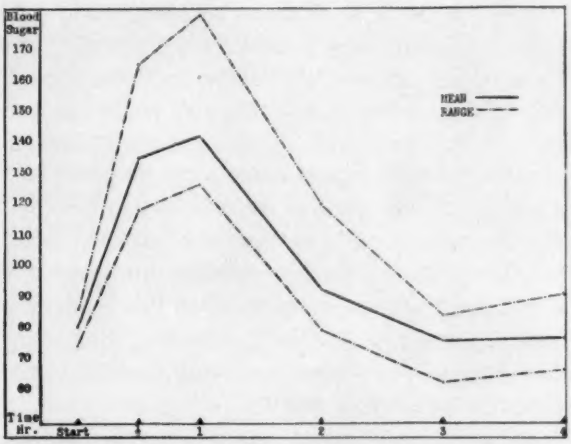

Chart 2.—The range and mean of the blood sugar values for 9 breast-fed infants. The mean fasting blood sugar level is 81.7 mg. per hundred cubic centimeters, and the mean maximum is 142.6 mg., a mean maximum rise of 60.9 mg. In 7 of the 9 infants the maximum blood sugar concentration was attained at one hour; 1 had values practically identical at one-half and at one hour, and 1 showed a drop of 15 mg. between the half-hour and the hour specimen. Six of the 9 infants showed the hypoglycemic reaction of Foster.

maximum level was delayed until one hour had passed. There are no significant differences in range or in mean fasting or mean maximum values between the two groups. The data are presented graphically in charts 1 and 2.

The two distinct configurations of both individual and average curves suggest that the carbohydrate of the diet may affect the dextrose tolerance of the newborn. Since the difference does not always coincide with the type of feeding, it may be a transitory condition, disappearing when mixtures of carbohydrates are added to the diet. The tendency apparently has not been noted by other workers, but fixed dosage and infrequent determinations might obscure such slight variations in response. Greenwald and Pennell [14] found lower average maximum values than are reported here. The range of response in their subjects was lower, and they obtained more uniform curves than those in the present study.

Charts 3 to 8 show the response of infants of diabetic mothers to the same test. Each is accompanied by notes concerning the condition of the mother, the condition of the infant after birth, the reaction of the infant to the test and other pertinent material.

The offspring of women with diabetes proved more difficult to test than the normal infants, feeding only when urged, regurgitating and in general reacting with distaste. Tests obtained early in the series did not include thirty minute determinations of blood sugar. Infants on a three hour feeding schedule were followed for a shorter period than that outlined. Most of the infants of diabetic mothers showed a smaller maximum rise than the controls, but this may be due to some variation in the technic of the test, such as slow ingestion or regurgitation. Granted that such technical factors exert some influence on the contour of the curve, the underlying cause of the difficulty in feeding seems to be the diabetes of the mother. I have observed that the infants of women with diabetes often present a feeding problem during the first few days of life. Randall and Rynearson [17] also noted this tendency; they mentioned difficulty in feeding in 3 of the 7 cases they discussed.

One patient (chart 7) presented a striking contrast to the group and is therefore considered more in detail.

The mother of the infant was mildly diabetic, with fasting blood sugar values only slightly above normal; the diagnosis of diabetes was made on the basis of an Exton-Rose dextrose tolerance test, which showed blood sugar levels of 104 mg. per hundred cubic centimeters at fasting, 191 mg. after thirty minutes, 222 mg. after one hour and 222 mg. after ninety minutes. Values given are for capillary blood and were obtained by the Folin-Malmros modified technic, according to which normal values for adults are from 70 to 90 mg. Her basal metabolic rate

17. Randall, L. M., and Rynearson, E. H.: Delivery and Care of the New-Born Infant of the Diabetic Mother, J. A. M. A. **107**:919 (Sept. 19) 1936.

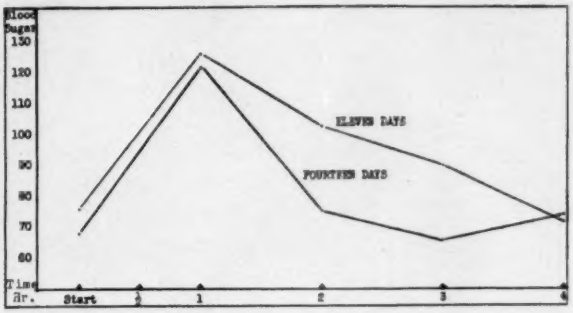

Chart 3.—Results of two dextrose tolerance tests, made at 11 and at 14 days of age, on the child of a woman with severe diabetes. The infant, a white boy, was born at term. The mother had received optimum care throughout pregnancy. The duration of her diabetes was ten years; it was controlled by insulin (40 to 60 units) and by diet. One previous child was living and well. After delivery, the infant had slight hypoglycemia, which was controlled by dextrose given subcutaneously. When tested at 11 days of age (weight, 3.6 Kg.) the baby took 63 cc. of a 10 per cent solution of dextrose in fifteen minutes, with great urging. There was no regurgitation. The urine gave a yellow-green reduction of Benedict's solution. At 14 days of age (weight, 3.64 Kg.) the infant took 65 cc. of a 10 per cent solution of dextrose in fifteen minutes, with great urging. There was no regurgitation. The urine reacted as before. (The case represented by this chart is reported by permission of Dr. F. S. Mowry and Dr. P. G. Albrecht.)

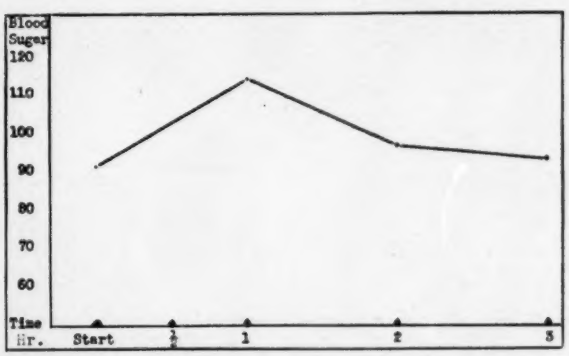

Chart 4.—Results of a dextrose tolerance test on a premature infant (seven and a half months' gestation) born to a woman with moderately severe diabetes, diagnosed during this pregnancy. The duration of the diabetes was unknown; it was controlled by insulin (15 units) and by diet for eight weeks. Six months after delivery the diabetes was more severe, requiring 25 units of insulin. The infant, a white boy, showed no reaction after delivery, which was by breech presentation. When tested at 5 days of age (weight, 2.49 Kg.) the baby took 45 cc. of a 10 per cent solution of dextrose in fifteen minutes, with urging. There was no regurgitation. The urine was not tested.

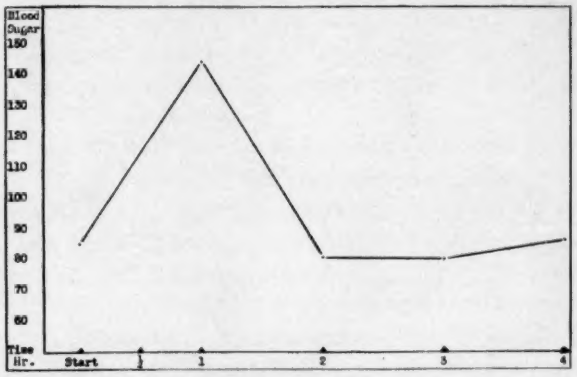

Chart 5.—Results of a dextrose tolerance test on a white baby boy, born at term by cesarean section to a woman with moderately severe diabetes. The duration of the diabetes was unknown, but the patient was on a self-imposed diet when pregnancy occurred. During the last five weeks of pregnancy she received treatment which included diabetic diet and 15 units of insulin. The mother died four days post partum from a heart attack. When tested at 13 days of age (weight, 3.14 Kg.) the infant took 53 cc. of a 10 per cent solution of dextrose in fifteen minutes, with urging. He regurgitated approximately 10 cc. of the solution. The urine was not tested.

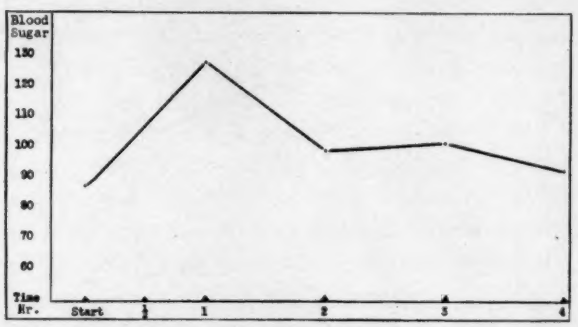

Chart 6.—Results of a dextrose tolerance test on a white baby girl, born to a woman with mild diabetes slightly after the date due, after induction of labor with a Voorhees bag. The duration of the mother's diabetes was unknown, as it was diagnosed during this pregnancy. She had ten weeks' control by diet alone. Five months post partum the diabetes was well controlled by diet alone, but the mother had the diabetic type of dextrose tolerance curve. The infant had no reaction after delivery. When tested at 6 days of age (weight, 3.65 Kg.) the baby took 65 cc. of a 10 per cent solution of dextrose in five minutes, all of which was retained. The urine showed no reduction.

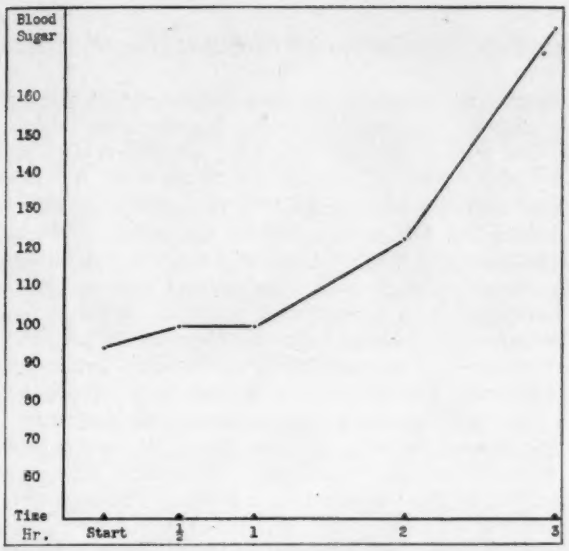

Chart 7.—Results of a dextrose tolerance test on a baby girl, white, born at term to a woman with mild diabetes. The duration of the diabetes, which was diagnosed during this pregnancy, was unknown. The mother had six weeks of dietary regimen. The reaction of the infant after delivery is discussed in the text. When tested at 8 days of age (weight, 2.47 Kg.) the baby took 40 cc. of a dose of 45 cc. in ten minutes. She regurgitated approximately 10 cc. The urine was normal when tested on two occasions.

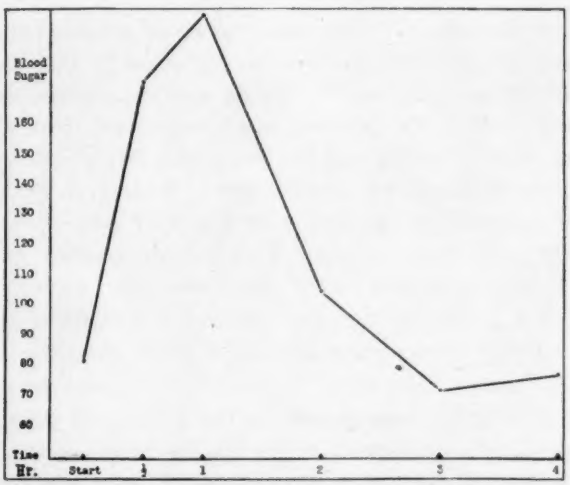

Chart 8.—Results of a dextrose tolerance test on a Negro baby, a boy, born to a woman with mild diabetes, diagnosed during pregnancy. The duration of the diabetes was unknown. The diabetes was uncontrolled, owing to lack of cooperation. The length of gestation was unknown, since the patient had not menstruated after her previous pregnancy. The infant had mild tremors which were easily controlled by feedings of Karo corn syrup mixed with water. When tested at 5 days of age (weight, 3.55 Kg.) he took 63 cc. of a 10 per cent solution of dextrose, with urging, in five minutes. He cried throughout the test and may have regurgitated a small amount of the solution. The urine showed slight green reduction.

was — 18 per cent; she claimed to be weak and stated that cuts and burns healed slowly. The diabetes was easily controlled by diet alone, and the patient had six weeks of care prior to delivery. The baby was delivered by breech extraction after a short labor; although born practically at term, it weighed 2,380 Gm. Numerous blood sugar values determined for the infant were, with two exceptions, higher than normal for the newborn. There was no fall to the normal level for newborn infants during the first few hours after delivery, and during the first day of life the baby showed signs of what might, without contrary laboratory evidence, have been interpreted as a hypoglycemic reaction. Pallor, convulsive tremors, subnormal temperature, unilateral facial paralysis, circumoral cyanosis and a cry of irritation were noted. The possibility of a birth injury seemed negligible because of the ease of delivery. The infant's condition was much improved by an infusion of 100 cc. of a 5 per cent solution of dextrose given subcutaneously. About twelve hours after this infusion the blood sugar was 85 mg. per hundred cubic centimeters, the lowest value obtained for this infant. Subnormal temperature, circumoral cyanosis and facial paralysis persisted for a few days; feedings were taken slowly, and usually some of the feeding was regurgitated, even after the infant's discharge from the hospital. During the stay at the hospital the baby received breast milk from a bottle; at home the formula was based on cow's milk fortified with Karo corn syrup, as advised by the dispensary. The dextrose tolerance curve was marked by a slow rise during the first two hours, with a definite increase to 179 mg. at the third hour. Immediately after this three hour test a feeding of breast milk was taken with less than the usual urging. At 3 months of age the infant still fed only with great urging, although the weight increased to 4,240 Gm. This case, without the repeated high values for blood sugar, might have been classified as a case of hypoglycemia.

Three of the normal infants who remained a sufficient time in the obstetric service were retested by a modification of the one hour, two dose test of Exton and Rose.[13] The dosage was determined as for the previous test; half of the dextrose was administered three and a half to four hours after a feeding and the remainder thirty minutes later. In each case some difficulty was experienced in feeding, as the infants were apparently temporarily satisfied with the first portion and took the second only with great urging. Two infants reached approximately the same levels as in the longer, one dose test, while a third, who regurgitated a portion of the dose, showed a maximum about 20 mg. per hundred cubic centimeters below the value obtained with the one dose test. Further tests were not carried out because most normal infants do not remain long enough in the hospital to permit two tests. It seems probable that because of the feeding habits of newborn infants more difficulty will be met in attempting to perform a two dose test.

SUMMARY

By the Jeghers-Myers modification of the Folin-Malmros ferricyanide micromethod, the blood sugar values of 16 normal newborn infants 5 to 10 days old ranged from 70 to 95 mg. per hundred cubic centimeters three and one-half to four hours after feeding, with a mean of 81 mg.

Dextrose tolerance tests were made on 15 normal infants. Oral administration of 1.75 Gm. of dextrose per kilogram of body weight, as a 10 per cent solution, with blood sugar determinations one-half, one, two, three and four hours after the midpoint of the period necessary for ingestion, produced an average maximum level of 143 mg. per hundred cubic centimeters. Two distinct types of curve were present; the blood sugar value of formula-fed infants reached a mean maximum of 143.2 mg. at thirty minutes, while that of breast-fed infants reached a mean maximum of 142.6 mg. at one hour.

Response to the dextrose meal was higher than in previously reported work; apparently these infants responded just as young adults do. The hypoglycemic reaction of Foster was encountered in 11 of the 14 babies tested.

Infants of diabetic mothers were more difficult to test than were the controls, and the curves produced seemed less reliable than those of the controls, owing to technical factors which could not be regulated. One infant who had previously showed the clinical signs of hypoglycemia had a strikingly erratic curve.

The Exton-Rose one hour, two dose test modified to the dose-weight principle was administered to 3 normal infants, but the nature of the divided dose leads one to believe this technic unsuitable for the newborn.

Case Reports

SURGICAL OBLITERATION OF A PATENT DUCTUS ARTERIOSUS IN A 7 YEAR OLD GIRL

ROBERT E. GROSS, M.D.

PAUL EMERSON, M.D.
AND
HYMAN GREEN, M.D.
BOSTON

The child with a patent ductus arteriosus usually suffers little or no incapacitation but is subject to certain dangers in later life. The arteriovenous communication between the aortic arch and the pulmonary artery is a definite hazard because of the possibility of (1) aneurysmal dilatation and rupture of the ductus or pulmonary artery, (2) thrombosis of the ductus with embolism, (3) subacute bacterial endocarditis or endarteritis and (4) cardiac decompensation resulting from overwork of the heart. Many persons with a patent ductus arteriosus live a long and useful life, but the chances of supervening bacterial endocarditis or cardiac failure are high. In a group of 92 patients who died of this lesion, Maude Abbott[1] found that the average age at which death occurred was 24. The seriousness of the prognosis makes worth while treating these children while they are in relatively good health and before fatal complications develop.

The surgical obliteration of a persistently patent ductus would appear to be a rational procedure provided the operative mortality could be kept relatively low. A suitable approach to the ductus region has been devised by working with postmortem human material and subsequently practicing the operative steps on dogs in the experimental laboratory.[2] The first two patients on whom this operation was undertaken showed remarkably little postoperative reaction and have had a striking improvement in their cardiovascular mechanisms.[3] The success with these

From the Surgical and Medical Services of the Children's Hospital and the Departments of Surgery and Pediatrics of the Harvard Medical School.

1. Abbott, M. E.: Congenital Heart Disease, in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1926, vol. 4, p. 207.

2. Gross, R. E.: A Surgical Approach for Ligation of a Patent Ductus Arteriosus, New England J. Med., to be published.

3. Gross, R. E., and Hubbard, J. P.: Surgical Ligation of a Patent Ductus Arteriosus: Report of First Successful Case, J. A. M. A. **112**:729 (Feb. 25) 1939. Gross, R. E.; Emerson, P., and Green, H.: Surgical Exploration and Closure of Patent Ductus Arteriosus: Report of Second Successful Case, Surgery **6**:201 (Aug.) 1939.

patients encouraged us to advise operation on a third, who is reported on here.[4] This child had definite evidence of a large ductus, as shown by the pulmonary congestion, the enlarged pulmonary artery and the low diastolic pressure. Operation appeared less dangerous than the complications which would probably ensue if the large ductus were left open.

REPORT OF A CASE

History.—F. S., a 7 year old girl, entered the hospital Nov. 2, 1938, for study of her cardiac condition. Her outpatient department record revealed the following findings: When she was 2 months old a loud murmur was heard at the cardiac apex. When she was 3 years old there was a rough murmur, which was thought to be loudest at the mitral area. This was continuous and was described as of a machinery type; it was accompanied by a thrill. The blood pressure at that time was 120 systolic and 40 diastolic. There were marked pulsations in all the extremities, with pistol shot pulsations over the major arteries of the arms and legs. When she was 3½ the murmurs and thrill were described as being most intense at the base of the heart. At that time an electrocardiogram was normal except for some slurring of the QRS complex in lead III. During her third and fourth years there were frequent complaints of pain in the chest and definite shortness of breath. When she was 4 the heart rate was 100 and she was irritable and tired easily. When she was 5 there was no complaint of pain in the chest, but there was still considerable dyspnea on exertion. When she was 6 prominent veins were noticed over the chest, and the blood pressure at this time was 110 systolic and 58 diastolic. Again there were pains in the chest following exercise. The child had gained weight but poorly. At no time had there been cyanosis. There had been occasional epistaxis. At no time had there been peripheral edema, orthopnea or frank cardiac decompensation.

Physical Examination.—The child was intelligent and cooperative. She was 46 inches (116.8 cm.) tall and weighed 42½ pounds (19.3 Kg.). She was somewhat small for her age but was fairly well developed and nourished. The respirations were normal. The heart rate was 95. The heart was somewhat enlarged toward the left. The cardiac action showed a heaving impulse and an overactive heart beat, imparting a shock to the precordium which was both palpable and visible. Palpation revealed a coarse thrill which was felt over the entire precordium but which was most intense in the second interspace to the left of the sternum. Auscultation revealed a loud continuous machinery type murmur, which was heard over the entire precordium but which was loudest in the pulmonic area. This murmur was transmitted with but slight diminution to the apex. It was loud in both axillas, particularly the left, and was prominent over the thorax posteriorly, particularly to the left of the spine. It was heard only faintly over the vessels of the neck. The second pulmonic sound was greatly accentuated and had a snapping quality. There was a collapsing type of peripheral pulse, and there was a definite visible pulsation in the nail beds. In the recumbent position the blood pressure in the right arm was 105 systolic and 50 diastolic, in the left arm 105 and 50, in the left leg 125 and 40, and in the right leg 130 and 44. There was no clubbing of the fingers or toes.

4. After the operation on this child, a fourth patient was successfully operated on (Gross, R. E.: Surgical Management of the Patent Ductus Arteriosus, with Summary of Four Surgically Treated Cases, Ann. Surg. **110**:321 [Sept.] 1939).

Laboratory Examination.—The urine was normal. The hemoglobin content was 90 per cent, and the red blood cell count was 5,090,000 per cubic millimeter. An electrocardiogram still showed splintering of the QRS complex in lead III but showed no other abnormality. Fluoroscopic studies of the heart showed a great increase in the pulsations of that organ, with an increased pulsation in the aortic arch and pulmonary artery. The latter vessel was distinctly larger than normal. The transverse dimension of the heart was 9.8 cm., and the internal diameter of the chest was 18.8 cm. (fig. 1). There was moderate perihilar congestion, and there was a definite hilar dance in the hilar arteries of the lungs.

Operation.—November 9, operation was undertaken (by R. E. G.) with the patient under cyclopropane anesthesia. A transverse, slightly curved incision was made just above the left breast, and the pectoral muscles were transected so as

Fig. 1.—Roentgenogram of the chest taken at a distance of 7 feet, showing (1) prominence of the left ventricle, (2) fulness of the pulmonary artery in the region marked by arrows and (3) congestion of the vessels in the lung fields. The transverse dimension of the heart was 9.8 cm. and the internal diameter of the thorax 18.8 cm.

to expose the third left interspace. The left pleural cavity was entered through the third space, and the third and second costal cartilages were cut so that the ribs might be retracted upward. The lung was collapsed and packed away inferiorly. The heart was seen to have a forceful and vigorous beat. Palpation revealed a marked thrill over the entire presenting portion of the heart, which was increased as the fingers were run up along the pulmonary artery. There was no thrill in the aortic arch when it was palpated. There was a moderate thrill on palpation of the ductus region, the greatest thrill being present in the pulmonary artery. The pleural covering of the mediastinum was now incised from the root of the lung upward for a distance of about 3 inches (7.6 cm.). After considerable time-

consuming dissection of fat, areolar tissue and vascular network, the sulcus between the aortic arch and the pulmonary artery was sufficiently cleared. The left recurrent laryngeal nerve was identified; it was traced downward and medially and led directly to a large patent ductus, which was 7 to 8 mm. in diameter and about 7 mm. in length. This vessel was about the size of the nearby left subclavian artery as it arose from the aortic arch and appeared to have a wall of about the same thickness. Great care was taken to dissect the areolar tissue posterior and medial to the ductus to avoid unnecessary bleeding. The left main bronchus was dissected away from the posteromedial aspect of the ductus by employing a right angle clamp to reach the posterior aspect of this vessel. A temporary ligature was then

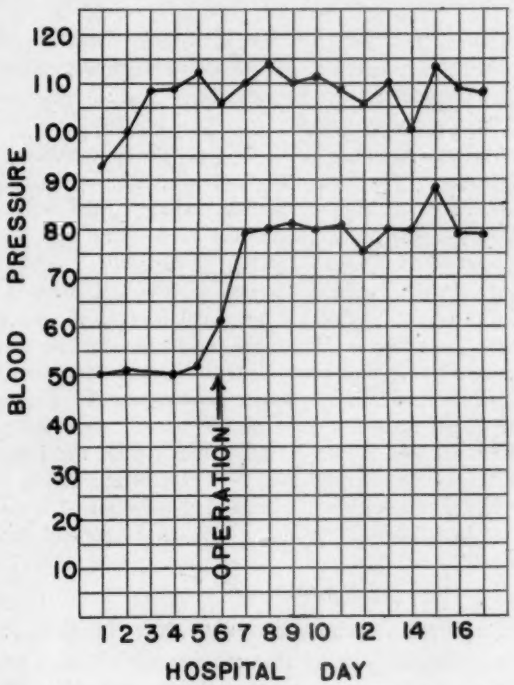

Fig. 2.—Daily blood pressure readings during the patient's stay in the hospital. Before operation the systolic pressure was normal but the diastolic pressure was lower than normal. After ligation of the patent ductus arteriosus the diastolic pressure rose, as indicated.

placed around the ductus and drawn up snugly. As soon as this was done there was a slowing of the heart rate from 100 to about 75. At the same time there was a diminution in the activity of the heart, so that it assumed a beat of normal magnitude and intensity. There was also an immediate rise of the diastolic pressure. This temporary ligature was left on for three or four minutes, during which time there was no embarrassment of the cardiovascular system. Indeed, there was marked improvement, as shown by the increase in the diastolic blood pressure, slowing of the heart and diminution in intensity of the cardiac beat. It was therefore decided to ligate the vessel permanently. This was done with two heavy braided waxed silk sutures, which were drawn down snugly into place to obliterate

the lumen of the vessel. When this was done, the thrill completely disappeared. Auscultation of the pulmonary artery with a sterile stethoscope had previously revealed a roaring continuous murmur, but now that the ductus was ligated this murmur had disappeared. Samples of blood were aspirated from the aortic arch, the ductus, the pulmonary trunk and the left pulmonary artery, both before and after the ductus was ligated, for study of the oxygen content in order that the output of the right and left ventricles might be subsequently computed. These studies, which are reported elsewhere,[5] showed a great decrease in the work of the heart and a concomitant increase in the peripheral circulation following ligation of the ducts. The pleural covering of the mediastinum was closed with interrupted sutures. The lung was now reexpanded, with positive pressure anesthesia. The chest was closed with continuous 00 chromic catgut to the lateral part of the pleura and the intercostal muscles. The fascial coverings of the pectoral muscles were approximated with interrupted catgut sutures, and the ends of the cut muscles were butted with interrupted silk mattress stitches. The subcutaneous tissues and skin were brought together with fine silk.

Postoperative Course.—After operation the child's convalescence was smooth and without complications. The wound healed by first intention. The left arm was kept immobilized for ten days to permit healing of the transected pectoral muscles. After this period, it was found that division of the muscles had not caused any impairment of movement or power in the arm.

The daily blood pressure readings showed a striking change in the diastolic level (fig. 2). Before operation this had averaged 50 mm. of mercury, but after ligation of the ductus there was an immediate and permanent rise to about 80 mm. The heart beat, which before had been so vigorous and overactive, was now of normal intensity. The thrill had completely disappeared. Postoperatively no murmurs could be heard over any part of the heart. Repeated roentgenologic examination of the chest and heart showed a clearing of the lung fields and a diminution in the transverse dimension of the heart from 9.8 to 8.8 cm. The pulmonary artery had decreased somewhat in size and showed a marked diminution in pulsation by kymographic tracings. The child's general health improved and she gained weight.

SUMMARY

A persistently patent ductus arteriosus after the first few years of life is an important cardiovascular abnormality which may lead to serious and even fatal complications in adolescence or adult life. The greatest of the impending dangers is subacute bacterial endocarditis. The next most important hazard is cardiac decompensation, which results from overwork of the heart produced by the arteriovenous communication.

Most patients with patent ductus arteriosus show little or no disability during childhood, but they are quietly laying the foundations for later trouble by building up atheromatous plaques in the pulmonary artery, which may later be the site of bacterial vegetations, or else they are so overexercising the heart that decompensation may occur one or two decades later. If operative ligation of the ductus can be performed early in life, the degenerative changes in the pulmonary artery should

5. Eppinger, E. C.; Burwell, C. S., and Gross, R. E.: Dynamics of the Circulation in Patients with Patent Ductus Arteriosus, to be published.

be arrested and the danger of subsequent bacterial endarteritis should be decreased. Likewise, closure of the arteriovenous shunt greatly reduces the work of the heart and should increase the cardiac reserve. The feasibility of such an operation is demonstrated by the fact that 4 patients have been successfully subjected to it without mortality and without complications. One of the cases is here reported. After operation there was (1) a rise in the previously low diastolic pressure, (2) disappearance of the precordial thrill, (3) disappearance of all cardiac murmurs, (4) a decrease in the size of the heart and (5) a decrease in the work of the heart. It therefore appears that in properly selected cases surgical obliteration of a patent ductus arteriosus is a rational procedure which has much to offer the patient.

721 Huntington Avenue.

REFRACTORY RICKETS

HARRY BAKWIN, M.D.

OSCAR BODANSKY, M.D.
AND
RICHARD SCHORR, M.D.
NEW YORK

The curative effect of vitamin D or ultraviolet irradiation on rickets in infants is one of the most constant phenomena in pediatric practice. In infants with tetany, for whom the influence of treatment on the serum calcium can be readily measured, the rise in the serum calcium level after adequate doses of viosterol or ultraviolet radiation occurs at a fairly regular rate of about 0.4 mg. per day. Exceptions are unusual.

After the second year of life the effect of antirachitic therapy is much less constant. The amounts necessary for cure are often considerably larger than during infancy, and the rate of healing is much slower. However, cases such as that to be described, in which extremely large amounts of vitamin D are necessary for cure, are extremely rare.

REPORT OF A CASE

W. D., a boy of 8 years, was first seen in April 1931 because of difficulty and pain on walking. He was born Sept. 4, 1922, the only child of German-American parents in moderate circumstances. Delivery was instrumental; the birth weight was 5 Kg., and the postnatal course was uneventful. The child was breast fed for eleven months. Administration of orange juice was started at the age of 5 months and of solid food at 9 months. A vitamin D supplement was not given during the first year of life.

At about the age of 3 months the boy began to have convulsions. They occurred daily, often several times on the same day, and usually lasted several minutes. They were preceded by a cry, there was no shaking and the child usually fell asleep afterward. They took place at any time of the day and in any place (as in bed or on the street) and were not associated with fever, temper tantrums or any season of the year. The attacks grew more frequent and more severe until the child was about 5 years old, at which time they ceased entirely; they had never recurred.

Shortly after cessation of the convulsions, when the patient was about 6 years old, he began to complain of pain in the lower extremities on exertion. He tired quickly and had difficulty going up and down stairs. He slept poorly, perspired freely and was constipated. At about this time he had diphtheria, measles, chickenpox and a tonsillectomy because of frequent attacks of tonsillitis. He was thought

From the Departments of Pediatrics and Pathology, New York University, and the Children's Medical Service, Bellevue Hospital.

to have rheumatic fever, but antirheumatic treatment was without effect. His diet was adequate and included a quart (946 cc.) of milk each day.

Examination (in April, 1931, two years after the onset of symptoms) revealed a blond, fair-skinned boy of good intelligence and normal behavior (fig. 1). The height and weight were within normal limits and the muscles firm and well developed. The patient showed moderate knock knee and a soft systolic murmur. There were well marked rounded swellings at the wrists and ankles and prominent enlargements at the costochondral junctions. The shape of the head was normal, and the teeth were well formed, with a few cavities.

Roentgenograms (fig. 2) showed the typical changes of rickets at the ends of the bones. The shafts at this time were well calcified. The serum calcium level was 11.1 mg. and the serum inorganic phosphorus level 1.9 mg. per hundred cubic centimeters.

Fig. 1.—W. D. in April 1931, at the age of 8 years, two years after the onset of his illness. Note enlargements at the wrists and ankles.

On April 7 the boy was admitted to Bellevue Hospital. He was 117 cm. in height and weighed 21 Kg. The urine and feces were normal. Renal function (phenolsulfonphthalein and Mosenthal tests) was normal, as were the carbon dioxide, the nonprotein nitrogen content of the blood and the blood pressure. A blood sugar curve at this time was normal, the value rising from 114 to 158 mg. per hundred cubic centimeters in one hour and falling to 110 mg. at the end of two hours. There were 3,800,000 red blood cells per cubic millimeter; the hemoglobin content was 65 per cent. Cod liver oil, exposure to sunlight and viosterol (60 drops, or 13,000 U. S. P. units of vitamin D), as well as 2 quarts (1,892 cc.) of milk, were given daily, and after the child's discharge the treatment was continued at home by the mother. The rachitic changes, however, persisted, and decalcification of the shafts became evident. Knock knee and difficulty in walking became worse. In September 1932 a bilateral tibial osteotomy for knock knee was performed. The fractures healed promptly.

The boy disappeared from observation until December 1933. Walking had become increasingly difficult. The swellings at the wrists and ankles were unchanged, but the costochondral enlargements were less pronounced, owing to retraction of the thoracic wall. Roentgenograms showed further decalcification involving all the bones of the skeleton. The value for serum calcium was 10.1 mg., inorganic phosphorus 1.9 mg. and phosphatase 45 units. Supplementary vitamin D had not been given in the interval. At this time, with test diets moderately high in calcium and phosphorus (Aub's diet C), there were slightly negative balances for both these elements. Ninety-six per cent of the excreted calcium was present

Fig. 2.—Roentgenogram of the forearm and wrist of W. D. made in April 1931. The epiphyses show flaring, fraying and some cupping. The shafts of the bones are well calcified.

in the feces and only 4 per cent in the urine, findings characteristic of rickets. The excreted phosphorus was divided approximately equally between stool and urine, as is normally the case. At this time the patient was not receiving vitamin D (table 1).

In January 1934 the boy was given 12 cc. of cod liver oil, 3 cc. of viosterol (30,000 units of vitamin D) and ultraviolet radiation daily. In spite of this intensive therapy, which was continued for several months, the condition continued to progress.

In January 1935 the boy, now 12 years old, showed progression of his symptoms. He could walk only a few feet. The arms could be moved freely, and he was

TABLE 1.—*Retention of Calcium and Phosphorus With and Without Supplements of Vitamin D* *

Date	Daily Dose of Vitamin D, U. S. P. Units	Diet	Calcium				Phosphorus			
			Intake	Output		Amount Retained	Intake	Output		Amount Retained
				Urine	Feces			Urine	Feces	
Dec. 9-11, 1933	0	Aub's diet C	1.43	0.09	1.97	—0.63	3.07	1.59	1.57	—0.09
Dec. 13-15, 1933	0	Aub's diet C	1.59	0.08	1.68	—0.17	3.03	1.56	1.56	—0.09
Jan. 28-30, 1935	40,000	Aub's diet B	2.00	0.22	0.58	1.20	1.75	1.21	0.26	0.28
April 28-May 1, 1935	110,000 since April 4, 1935	Aub's diet B	2.08	0.12	0.77	1.19	1.83	1.18	0.54	0.11

* All metabolic data are calculated for three day periods and expressed in grams.

mentally alert and in good spirits, participating, within the limits of a wheel chair, in the activities of the ward. The bones showed advanced osteoporosis, as well as the characteristic changes of rickets at the ends. The cortices were thin and poorly defined in the upper extremities, where the bony trabeculations were prominent. The bones of the lower extremities, particularly the tibias, showed a ground glass appearance, which persisted and which was probably associated with the lack of use of the lower extremities. The value for serum calcium was 10.4 mg., for inorganic phosphorus 1.5 mg. and for phosphatase 46 units.

At this time, while the patient was receiving 4 cc. of viosterol (40,000 units of vitamin D) daily, balance studies showed good retention of both calcium and phosphorus (table 1). Moreover, the proportion of calcium excreted in the stool had diminished. Though this favorable balance was also observed in a second period (April 1935), it was not accompanied by any demonstrable improvement in the patient's condition. For three weeks before the last balance study, in April, 1935, the boy had received 110,000 units of vitamin D daily in viosterol.

On Feb. 18, 1935, the value for plasma p_H was 7.28, for plasma sodium chloride 548 mg. per hundred cubic centimeters, for serum proteins 4.9 Gm. per hundred cubic centimeters and for total base 141 milliequivalents per liter. The hemoglobin content varied from 9.6 to 10.2 Gm. and the red blood cell count from 3,560,000 to 3,900,000. The white blood cell and the platelet count were normal. The Wassermann reaction was negative, the basal metabolic rate —9 per cent and the electrocardiogram normal. The nonprotein nitrogen, sugar and cholesterol values of the blood were normal. Phenolsulfonphthalein and Mosenthal tests and routine examinations of the urine gave normal results. On later examinations the values for plasma p_H and for sodium chloride, proteins and total base in the serum were normal.

On February 1 the boy was given the ward diet and 4 cc. of viosterol daily. After one month there was no change in his condition. On March 1 the administration of viosterol was continued, and 15 Gm. of calcium phosphate daily was added. After a month there were stalactite-like deposits of calcium in the wide rachitic preparatory zones at the wrists. This was definite but not marked.

On April 1 sodium bicarbonate was added to the other medication, but the amount was not sufficient to alkalinize the urine. At this time the vitamin D supplement was increased to 110,000 units. The roentgenograms on May 1 showed distinct improvement; the calcification had extended down from the shaft, in some places all the way to the epiphysial centers. The osteoporosis of the shafts, however, remained unchanged. The serum calcium value rose to 11.1 mg. and the inorganic phosphorus content to 2.7 mg. per hundred cubic centimeters.

After May 1 the dose of viosterol was reduced to 40,000 units daily, and administration of dicalcium phosphate ($CaHPO_4 : 2H_2O$), 15 Gm. daily, and sodium bicarbonate, 12 Gm. daily, was continued. However, there was no further improvement, and on June 30 the sodium bicarbonate therapy was discontinued.

Despite the fact that the boy had received regularly at least 20,000 units of vitamin D daily between February 1 and August 1, his condition became steadily worse. It became gradually more and more difficult for him to get about. There seemed to be muscular weakness, although the muscles appeared firm. In November riding a bicycle with the rear wheel elevated to exercise the lower extremities was attempted but had to be abandoned because the effort was too great for the patient. He was getting shorter and had to be carried for even a short distance. The height was 118.8 cm., an increase of only 1.8 cm. during the four and a half years of observation. During this period the weight had increased from 21 to 25.7 Kg.

In December drisdol (30 drops daily, or 7,500 units of vitamin D) was substituted for the viosterol but without favorable effect. Calcium gluconate combined with crystalline vitamin D in propylene glycol (drisdol) was also ineffective.

A blood sugar curve in January 1936 showed a value during fasting of 133 mg. The sugar level rose to 195 mg. at the end of one hour and was still 188 mg. at the end of two hours. The urine showed a trace of reducing substance with Benedict's solution. One year later the blood sugar curve was normal.

In February 1936 the patient was given 4 cc. of viosterol daily (40,000 units of vitamin D); after one week his blood serum was tested for its vitamin D content by Dr. Josef Warkany,[1] who reported the content to be approximately 830 rat units of vitamin D per hundred cubic centimeters or twenty times that of a normal person. Dr. Warkany stated that this was the highest value he had up to that time observed in a human being. Antirachitic treatment was therefore discontinued (except for exposure to sunlight), and the boy was given 12 Gm. of calcium gluconate daily by mouth. There was no noticeable effect.

On April 22 the boy's condition and the roentgenograms showed that no change had occurred since examinations made within the preceding year or two. He was unable to walk more than a few steps. The value for serum calcium was 10.7 mg., inorganic phosphorus 1.8 mg., phosphatase 49 units, total cholesterol 200 mg., plasma sodium chloride 576 mg., blood nonprotein nitrogen 28 mg. and blood sugar 110 mg. The patient was given intravenously 12 cc. daily of a 10 per cent solution of calcium gluconate containing about 120 mg. of calcium. One week later the value for serum calcium was 10.3 mg., inorganic phosphorus 2.1 mg. and phosphatase 51 units; two weeks later the calcium level was 9.9 mg., inorganic phosphorus 1.7 mg. and phosphatase 39 units.

In February 1937 the parathyroid regions were explored, but no parathyroid tissue was found. From January to April the serum phosphorus rose to between 3.5 and 4.5 mg. and the phosphatase level fell from 77 to 31 units, although no supplements of vitamin D were given.

In March administration of dihydrotachysterol was begun. Thirty cubic centimeters was given in approximately sixty days. It was first combined with dicalcium phosphate, but the boy complained that the latter caused nausea, abdominal pain and anorexia. It was consequently discontinued after a few weeks, and thereafter the child felt well. The rachitic manifestations remained clinically unchanged. Routine examination showed the urine to be normal, except for a trace of reducing substance on one occasion. The roentgenograms showed active calcification in the rachitic preparatory zones, but decalcification of the shafts persisted unchanged. In May, after the period of treatment, the value for serum calcium was 9.7 mg., inorganic phosphorus 1.6 mg. and phosphatase 73 units.

During the summer the boy received no special treatment except for administration of a tablespoonful of cod liver oil and 1,000 to 1,500 cc. of milk daily. The calcium in the rachitic preparatory zones largely disappeared, and in September a second course of treatment with dihydrotachysterol was begun, but without favorable effect.

At no time did abnormal calcifications appear in the internal organs.

In December, after the discovery by Albright, Butler and Bloomberg [2] that the condition in a case similar to ours could be cured by massive doses of vitamin D, our patient was given 1,000,000 units of the vitamin daily. Before treatment was

1. Warkany, J.: Estimation of Vitamin D in Blood Serum, Am. J. Dis. Child. **52**:831 (Oct.) 1936.

2. Albright, F.; Butler, A. M., and Bloomberg, E.: Rickets Resistant to Vitamin D Therapy, Am. J. Dis. Child. **54**:529 (Sept.) 1937.

started, the boy was unable to stand. There were contractures at the hip joints, knees and elbows. The chest was deep and narrow and the vertebral column kyphotic. The value for serum calcium was 9.6 mg., phosphorus 2.1 mg. and phosphatase 76 units. The roentgenograms showed florid rickets without evidence of healing. There was marked generalized osteoporosis.

After the administration of these large doses of vitamin D, evidence of healing appeared promptly in the roentgenograms. Four weeks after treatment was begun the serum phosphorus level was 3 mg. The close relation between treatment and the hematologic and roentgen findings is shown in table 2. By April 1938, after

Fig. 3.—Roentgenograms of the forearm, wrist and leg of W. D. made in December 1937, eight years after the onset of the rickets. The epiphyses are irregular and show some deposition of calcium in the rachitic zone. The bones, particularly of the leg, show marked osteoporosis.

four months of treatment, the rachitic changes at the ends of the bones were practically healed.

Orthopedic treatment for the correction of the rachitic deformities was begun in March. By July the boy was able to walk with crutches. The contractures at the hips, knees and elbows were corrected. The patient was markedly dwarfed, measuring only 132 cm. in height, in contrast to the average of 165 cm. for his age.

In July, while he was receiving 440,000 units of vitamin D daily, the serum calcium level rose to 14.4 mg. per hundred cubic centimeters and phosphorus to

6.7 mg. At the same time the serum phosphatase level fell to 7.8 units. No symptoms, however, were associated with the hypercalcemia, the boy's feeling of well-being, appetite, activity and alertness being unimpaired.

The dosage of vitamin D was immediately reduced to 110,000 units, and three weeks later the serum calcium level was 12.2 mg. and the phosphorus 4.2 mg. Administration of vitamin D supplements was discontinued. After August the boy was able to walk about without assistance and seemed well except for his short stature and bilateral coxa valga.

In October, after nine weeks without any supplementary vitamin D but with free exposure to sunlight, the roentgenograms showed distinct fuzziness at the distal

TABLE 2.—*Effect of Varying Doses of Vitamin D (Calciferol) on the Blood Calcium, Phosphorus and Phosphatase*

Date	Serum Calcium Mg. Per 100 Cc.	Serum Inorganic Phosphorus, Mg. Per 100 Cc.	Serum Phosphatase Units	Daily Vitamin D Supplements, U. S. P. Units	Stage of Rickets (Roentgen)
1937					
May 19	9.7	1.6	73	None	No healing
Sept. 10	9.8	1.5	67	None	No healing
Dec. 13	9.6	2.1	76	1,000,000 started	No healing
1938					
Jan. 10	9.9	3.0	77	1,000,000	Healing
Feb. 1	10.3	3.5	54	1,000,000	Healing
March 8	10.3	3.9	48	1,000,000	Healing
April 3	....	...	..	440,000 started	Healing
April 19	10.5	4.5	31	220,000 started	Healing
May 20	10.1	4.5	30	440,000 started	Healed
July 29	14.4	6.7	8	110,000 started	Healed
Aug. 17	12.2	4.2	..	Discontinued	Healed
Oct. 15	10.2	2.1	40	110,000 started	Active
Dec. 1	10.7	2.4	40	220,000 started	Active
1939					
Jan. 6	10.7	2.6	34	330,000 started	Active
Feb. 14	10.6	3.4	22	440,000 started	Active
April 3	10.5	3.8	17	440,000 started	Healing

ends of the radius and ulna. The value for serum calcium was 10.2 mg., inorganic phosphorus 2.1 mg. and phosphatase 40 units. A daily supplement of 110,000 units of vitamin D was then given. After six weeks the roentgen appearance of the bones showed continued rachitic activity, and the hematologic values were unchanged. The daily dose of vitamin D was consequently increased by 110,000 units at monthly intervals, and it was not until the boy was receiving a daily supplement of 440,000 units that the rickets was completely healed (table 2), although the serum phosphatase level was still elevated to 17 units after six weeks of this dosage. Free exposure to sunlight and ultraviolet radiation, together with a diet including large amounts of various fish containing vitamin D, was then prescribed in an effort to reduce the large amounts of viosterol necessary to prevent recurrence. The patient of Albright, Butler and Bloomberg required a daily supplement of about 150,000 units of vitamin D for maintenance (cited by Eliot and Park [3]).

3. Eliot, M. M., and Park, E. A.: Rickets, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1938, vol. 1, chap. 36, p. 1.

Fig. 4.—W. D. in 1938, at the age of 16 years, after rachitic healing. The height was 132 cm.

Fig. 5.—Roentgenogram of W. D. made in July 1938, showing complete healing after massive doses of vitamin D.

In brief, a white boy, after an infancy and an early childhood normal except for repeated convulsions of undetermined origin, began at the age of 6 years to suffer from difficulty in walking. These symptoms became more severe, and at the age of 8 years, when the child was first observed, he showed swellings at the wrists, ankles and costochondral junctions identical with those seen in rickets during infancy. Roentgenograms at this time showed the changes at the ends of the bones characteristic of rickets. The shafts were well calcified. The value for serum calcium was about 11 mg. and for inorganic phosphorus about 2 mg. Renal function was normal and remained so during the entire period of observation.

Despite treatment with vitamin D in fairly large amounts (up to 40,000 units a day), ultraviolet radiation, calcium diphosphate, calcium gluconate given by mouth and intravenously, alkalis and dihydrotachysterol, the boy became progressively worse, until he was finally unable to stand without support, and the roentgenograms showed progressive decalcification of all the bones. The parathyroid regions were explored, but no parathyroid tissue was found. Examination of the blood by Dr. Warkany following administration of viosterol showed that large amounts of vitamin D were being absorbed.

Throughout most of the patient's course the roentgenograms showed some calcium deposited in the rachitic preparatory zones at the ends of the bones. The amount varied, but decalcification of the shafts persisted, and no continued clinical improvement could be induced.

During the seven years that the boy was under observation the serum calcium fell from an initial value of 11 mg. to about 10 mg. and the serum phosphorus from 2 mg. to 1.5 mg. The value for serum phosphatase, about 45 units in 1933, rose to over 70 units in 1937.

When the patient was receiving no extra vitamin D the calcium and phosphorus balances showed poor retention, most of the ingested calcium being lost in the stool; after large dosages of vitamin D (40,000 and 110,000 units daily) there was good retention of calcium and phosphorus. A blood sugar curve in 1931 was normal; a second test in 1936, showed a diabetic sugar curve; a third test, in 1937, showed again a normal curve.

In February 1935 the boy had acidosis with a reduction in his plasma p_H, total base, serum proteins and plasma chlorides. A few weeks later these values were normal, and they have remained so.

After the administration of massive doses of vitamin D (1,000,000 units daily) the rachitic changes healed promptly and the serum calcium, phosphorus and phosphatase returned to normal levels. The boy remained normal except for his rachitic deformities, but it was necessary for him to continue to take large amounts of vitamin D to prevent relapse.

COMMENT

A boy with rickets requiring massive doses of vitamin D for cure has been described. The case apparently falls into a small but fairly well defined group, examples of which have been described by Albright, Butler and Bloomberg [2] and by Eliot and Park.[3]

The case represents an interesting anomaly in the metabolism of vitamin D. Under ordinary circumstances a regular diet and exposure to sunlight are sufficient to prevent rickets in a child of 8 years. Yet in our patient, despite a diet which contained a quart of milk a day and despite exposure to sunlight, there developed severe rickets, which was cured only when large amounts of vitamin D were given. The concept of vitamin D deficiency must be broadened to include the factor of dosage, since what may be an adequate amount for one child may be without effect for another. It is worthy of note that in the 3 cases thus far reported the metabolic anomaly made its appearance after the first year of life, when susceptibility to rickets is ordinarily greatest.

The fact that the absorption of large amounts of vitamin D by these patients was without effect on the rickets indicates that vitamin D itself is ineffective as an antirachitic factor. It is possible that this vitamin, like carotene, must be converted in the body before it becomes biologically active or that some other mechanism is deficient. Since cod liver oil and ultraviolet irradiation were also ineffective, the metabolic difficulty is not confined to the conversion of calciferol alone.

SUMMARY

A boy contracted rickets at the age of 6 years. The disease was characteristic, clinically and roentgenologically, and the blood showed a marked reduction of phosphorus and increase in phosphatase. Almost all the calcium was lost from the body in the stools.

Doses of vitamin D up to 40,000 units daily failed to cure the rickets.

Examination of the blood while the disease was active showed that large amounts of vitamin D were being absorbed.

With massive doses of vitamin D (1,000,000 units, equal to 100 cc. of viosterol) the rickets healed promptly.

Withdrawal of vitamin D resulted in recurrence of the rickets. A daily supplement of about 440,000 units of vitamin D was necessary for maintenance.

The large amounts of viosterol used were supplied by Mead Johnson & Co. Dicalcium phosphate (D.C.P. 340) was contributed by Parke, Davis & Co. and calcium gluconate by Sandoz Chemical Works, Inc. Dihydrotachysterol was obtained through the Winthrop Chemical Co., Inc.

PRODUCTIVE AORTITIS WITH MULTIPLE ANEURYSMS IN A CHILD

BENJAMIN H. NEIMAN, M.D.
CHICAGO
AND
MEYER B. MARKS, M.D.
MIAMI BEACH, FLA.

Changes of the blood vessels in congenital syphilis were first described in the English literature by Barlow,[1] in 1877. Although many observers have reported congenital syphilitic aortitis in young children and in adolescents (syphilis hereditaria tarda), the clinical aspects rather than the pathologic changes seem to have been stressed. Since in older children congenital syphilitic aortitis is uncommon, only 14 cases having been reported in the literature, we submit the following report of a case in which the anatomic observations were suggestive of this condition.

REPORT OF A CASE

History.—A 10 year old white girl was first admitted to the Cook County Hospital on March 14, 1935. Her parents were natives of Poland and unable to speak English. The patient stated that she had been in good health until September 1934, when she was taken to a physician because of a pain in her side. A diagnosis of pulmonary tuberculosis was made, and she was referred to a clinic. She made regular visits to the dispensary and was then sent to the hospital as having active pulmonary tuberculosis. She had been at home since her first visit to the dispensary. In spite of restricted activity she had lost 5 pounds (2.3 Kg.) in weight and complained of fatigue and loss of appetite.

Physical Examination.—The child was anemic and poorly nourished, with a rather full face, thin body and thin extremities. The temperature, pulse and respiration were normal. Over the face, the buttocks and the tibias there were pustules with necrotic centers which varied from pinhead to hazelnut in size and which were discrete and firm. There was diminished resonance in the base and in the upper third of the right lung posteriorly. There was also increased vocal and tactile fremitus over the lower third of the right side of the chest. No rales were audible. The heart was within normal limits, and no murmurs were elicited. An electrocardiogram showed low voltage. The edge of the liver was at the costal margin, and the spleen was not palpable. The reflexes were normal. Examination of the blood showed 3,420,000 red blood cells and 12,260 white blood cells, with 68 per cent neutrophils, 30 per cent lymphocytes and 2 monocytes. The Mantoux

From the Pathologic Institute, Cook County Hospital, Dr. R. H. Jaffé, director, and the Pediatric Service of Dr. J. Greengard. (Dr. Jaffé died Dec. 17, 1937.)

1. Barlow: Tr. Path. Soc. London **28**:287, 1877.

test was positive at 1:10,000. The urine was normal. The Wassermann test of the blood was negative.

The diagnosis made at this time was pulmonary tuberculosis with papulonecrotic tuberculids. A roentgenogram of the lungs revealed several calcified lesions, interpreted as tuberculous.

Course.—The patient showed no change until November 1935, when she began to have attacks of dyspnea, weakness and slight elevation of temperature in the evening. There was a striking discrepancy between the appearance of the head and neck and that of the rest of the body. Both the face and neck appeared swollen and full. The lips were swollen and cyanotic, the veins of the neck were engorged, and the eyes were slightly prominent. Elsewhere there was no edema, and the skin was pale except around the fingers and toes, where moderate cyanosis and definite clubbing were seen. The radial pulse of the right arm was palpable and strong. The radial, the brachial and the axillary pulse of the left arm were entirely absent. The blood pressure in the right arm was 120 systolic and 80 diastolic; in the left the pressure could not be obtained. There was marked, heaving precordial pulsation, and the cardiac dulness was transversely widened.

On reexamination the roentgenograms of the chest were now seen to show a well defined mass in the mediastinum which projected into the upper field of the left lung and seemed to increase gradually in size in succeeding films. The diagnosis made at this time was expanding neoplasm in the upper mediastinum, compressing the great vessels and resulting in venous stasis of the head and neck and compression of the left subclavian artery. Lymphosarcoma was thought to be the most plausible classification of the neoplasm, but a dermoid cyst or teratoma of the mediastinum and Hodgkin's disease were also considered as possibilities. Biopsy of a cervical lymph node revealed caseous tuberculosis. The face became increasingly swollen and engorged, and the cyanosis and dyspnea increased. The patient became progressively worse, bronchopneumonia developed, and she died on Dec. 18, 1935, nine months after entrance into the hospital and fifteen months after the appearance of symptoms.

Further history obtained from the father revealed that the mother of the patient had had 15 pregnancies. Eight children were living at the time the patient was admitted into the hospital, and 5 were dead. Two miscarriages had occurred spontaneously, one twenty years earlier, at two to three months' gestation, and the other two years earlier, at two months' gestation. Of the dead children, the supposed cause of death in 4 was pneumonia and in the fifth, "paralysis of the brain." Their ages had ranged from 18 months to 11 years. All the living children were said to be in good health. The oldest child was 15 years of age and the youngest 6 months. The Wassermann and Kahn tests of the father and mother were negative.

Autopsy.—The postmortem examination revealed generalized anasarca, a calcified primary tuberculous lesion in the apex of the upper lobe of the left lung, suppurative blepharitis of the left eye, hydropericardium, ascites, bilateral hydrothorax and bilateral fibrinous pleuritis. Endocarditis minima was present on the aortic valve, and there was an anemic infarct of the right kidney. The heart showed left ventricular hypertrophy and sclerosing aortitis of the ascending and the thoracic portion, with formation of four aneurysms and compression of the left subclavian artery by one of these aneurysms.

The heart, including the thoracic aorta, weighed 345 Gm. The wall of the left ventricle measured 12 mm. and that of the right ventricle 3 mm.; the myocardium was light purple-gray-brown, soft and friable. The longitudinal diameter of the left ventricle was 70 mm., and the transverse diameter was 95 mm.

At the valve the aorta measured 50 mm. in circumference. The leaflets were thin, and on the free margin of the posterior leaflet were single pinpoint-sized translucent nodules. The wall of the aorta was thickened in places up to 5 mm. The intima in numerous areas was wrinkled and puckered. Posterior and lateral to the origin of the left subclavian artery and slightly compressing it there was an outpouching of the wall 2 cm. in diameter. The intimal lining of the pouch was extremely wrinkled, and in the lumen there was an adherent purple-gray blood clot. The sinus of Valsalva of the right aortic leaflet revealed an aneurysmal outpouching 12 mm. in diameter. Above the middle leaflet there was an 8 mm. outpouching, and a fourth outpouching 9 mm. in diameter was present 4 cm. above the valve. The thoracic aorta showed similar wrinkling and puckering, and in the lowermost portion there were two areas 2 cm. long in which the intima was covered by adherent blood clots. In these areas the intima was roughened. The circumference of the thoracic aorta was 62 mm.; that of the abdominal aorta, 30 mm. At and below the level of the diaphragm the intima was smooth.

Microscopic Examination.—The intima of the aorta (fig. 1) was thickened. It consisted of a moderately cellular connective tissue, the ground substance of which occasionally showed a slight affinity to the hematoxylin stain. Interlacing with the connective tissue fibrils were isolated smooth muscle fibers which in the Van Gieson-stained sections stood out clearly as brass-yellow fusiform cells against the purple-red collagenous tissue. There were also fine elastic fibrils in the thickened intima. The internal elastic membrane was often interrupted, and where it had been preserved it was broken up into several wavy parallel layers. The media was severely altered. Dense scar tissue which seemed to be derived from the sclerosed adventitia separated the muscle bundles and often replaced them entirely, so that the entire wall of the aorta consisted only of connective tissue interspersed with the fine elastic fibrils described in the intima. In some areas where the scarring was less advanced, capillaries surrounded by fibrocytes and small round cells were seen forcing their way in perpendicular direction deep into the media, often reaching the intima. The adventitia was thick and composed of a dense connective tissue with small focal accumulations of lymphocytes. On the thickened intima deposits of blood platelets and of white and red blood cells were found. Many sections from various areas of the aorta were stained according to Levaditi's method, but no spirochetes could be found.

In the left ventricle of the heart (fig. 2) the muscle fibers were thicker than normal, and their nuclei were irregular in shape and rich in chromatin. The endocardium was slightly thickened.

COMMENT

The interesting point in the microscopic examination of the aorta was that all the characteristics of syphilitic aortitis as observed in the acquired form of the disease were seen to be present. The degeneration of the media with secondary fibrosis, the fibrotic thickening of the intima, the proliferation of the vasa vasorum with surrounding inflammatory infiltrations and the diffuse sclerosing inflammation of the adventitia all pointed to the syphilitic nature of the disease. This was further supported by the site of the lesion in the aorta.[2]

2. (*a*) Heller, A.: Verhandl. d. deutsch. path. Gesellsch. **2**:346, 1899. (*b*) Straub: ibid. **2**:351, 1899.

The aneurysms were confined to areas of localized tissue change which could not withstand the pressure within the vessel. That chronic inflammatory changes were going on in the aortic wall was seen in the destruction of the elastic and muscle fibers of the media, and that the process was chronic was demonstrated by the thickened intima. These features were all in accord with a syphilitic involvement of the aorta.

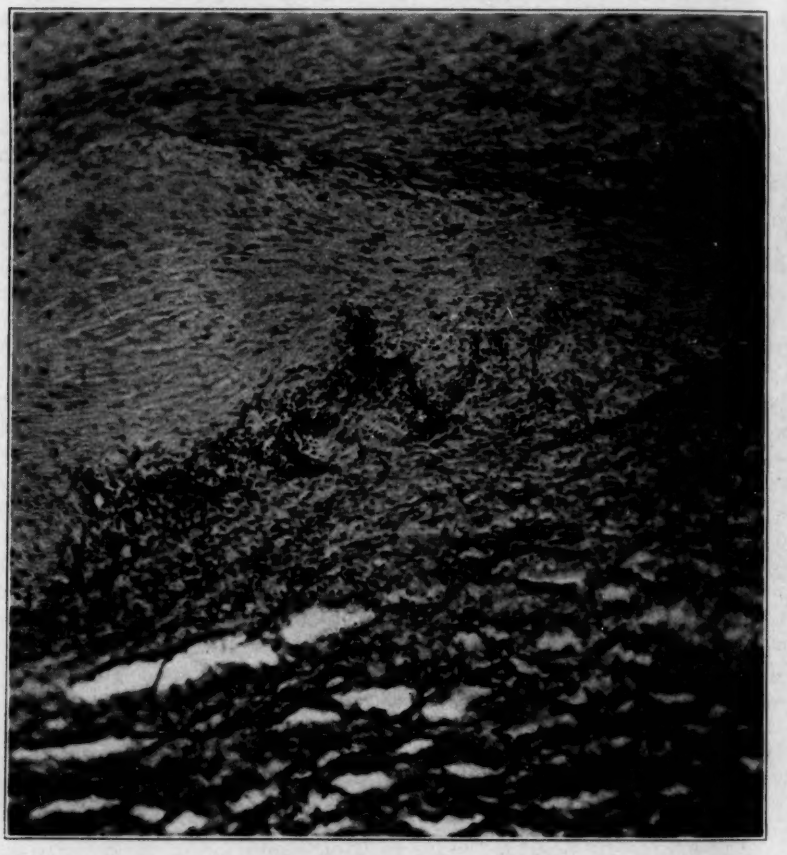

Fig. 1.—Section of the aorta showing productive inflammation (× 100).

Rheumatic fever, too, quite frequently leaves its mark on the large arteries, as has been described by one of us (Neiman [3]). Although inflammatory changes in the aorta were suspected in the course of rheumatic fever many years ago (Bouillaud,[4] 1840; Roger,[5] 1863;

3. Neiman, B. H.: J. Lab. & Clin. Med. **19**:929, 1934.

4. Bouillaud, J. B.: Traité clinique du rhumatisme articulaire, et de la loi de coïncidence des inflammations du cœur avec cette maladie, Paris, J. B. Bailliére, 1840.

5. Roger: Bull. Soc. méd. d. hôp. de Paris **5**:499, 1863.

Lelong,[6] 1869), no sustained effort to define the histologic features was made until the work of Klotz,[7] in 1912.

Pappenheimer and Von Glahn [8] found the distinctive lesion of the aorta in rheumatic fever to be a scar, roughly the shape of an inverted wedge, often acellular and located in the region of the nutrient vessels of the media. This type of arterial lesion was not found in a comparative study of nonrheumatic conditions. In some cases they found in the aortic adventitia specific changes consisting of the presence of

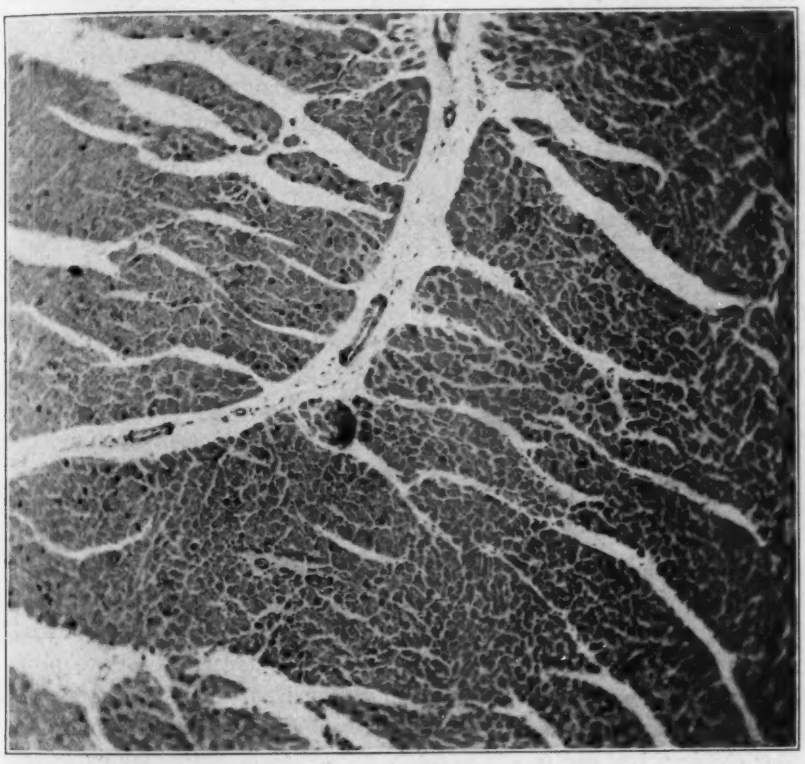

Fig. 2.—A representative field of the myocardium showing no inflammatory changes (× 125).

typical Aschoff cells, showing, however, little tendency toward grouping. They regarded these cells as diagnostic.

In our case, although rheumatic disease must be considered an etiologic possibility, there are several important factors which seem to

6. Lelong, M.: Etude sur l'artérite et sur la phlébite rhumatismale aiguë, Thesis, Paris, no. 99, 1869.

7. Klotz, O.: Tr. A. Am. Physicians **27**:181, 1912.

8. Pappenheimer, A. M., and Von Glahn, W. C.: J. M. Research **44**:489, 1924.

indicate that it did not play a role in the initiation of the arterial changes. In addition to the histologic character of the changes in the aorta, which did not resemble those seen in rheumatic fever, the severity of the process pointed toward syphilis. Although aneurysms are seen in rheumatic aortitis, they are distinctly less common than in syphilitic arteritis. In most cases of rheumatic arteritis the changes were seen in the cardiac valves, in the myocardium or in both. In our case no such changes were found. Finally, the history is negative for rheumatic fever. Although the history of the patient and her family does not denote syphilis, it is not unusual for a patient and other syphilitic members of a family to be as unaware of the presence of syphilis or of having contracted it as they are of having had some form of rheumatism.

After Doehle [9] and later Benecke,[10] Baumgarten,[11] Heller [2a] and Straub [2b] clearly established the relationship between acquired syphilis and aortitis, Hennig [12] and Mraček [13] described lesions in the aorta suggestive of aortitis in infants dead of hereditary syphilis. Rach and Wiesner [14] noted that 16 of 27 fetuses examined showed some aortitis and demonstrated Spirochaeta pallida in 4 of the 16 cases of aortitis. Rebaudi [15] found S. pallida in the three layers of the aorta of 5 syphilitic fetuses examined. Stolkind [16] up to 1920 had been unable to find in the literature any reference to a case in which spirochetes had been seen in the aorta of a child of more than 1 year of age with congenital syphilis. Klotz [17] showed both macroscopically and microscopically that the same changes that occur in the aorta in acquired syphilis may occur in that vessel in congenital syphilis. Klotz suggested that the healed lesions of hereditary syphilis may later give rise to a mistaken diagnosis of acquired syphilitic aortitis in the adult.

Although, as we have stated, many cases of congenital syphilitic aortitis in young children and adolescents (syphilis hereditaria tarda) have been recorded in the literature, the clinical aspects rather than the pathologic anatomy seem to have been emphasized. Stolkind stated that up to 1920 the conditions described as hereditary syphilitic aortitis in older children had not been absolutely proved to be that. He expressed the belief that such criteria as a family history of syphilis (in an

9. Doehle, P.: Ein Fall von eigentümlicher Aortenerkrankung bei einem Syfilitischen, Inaug. Dissert., Kiel, Lipsius u. Tischer, 1885; cited by Schulte, K.: Ztschr. f. Kreislaufforsch. **22**:753, 1930.

10. Benecke: Verhandl. d. deutsch. path. Gesellsch. **2**:365, 1899.

11. Baumgarten: Verhandl. d. deutsch. path. Gesellsch. **2**:364, 1899.

12. Hennig: Jahrb. f. Kinderh. **30**:106, 1890.

13. Mraček, F.: Arch. f. Dermat. u. Syph., 1893, supp., p. 279.

14. Rach, E., and Wiesner, R.: Wien. klin. Wchnschr. **20**:521, 1907.

15. Rebaudi, S.: Monatschr. f. Geburtsh. u. Gynäk. **35**:681, 1912.

16. Stolkind, E. J.: Brit. J. Child. Dis. **17**:126, 1920.

17. Klotz, O.: J. Path. & Bact. **12**:11, 1907.

isolated case), Hutchinson's teeth and a positive Wassermann reaction are insufficient for the diagnosis of congenital syphilis.

Schulte,[18] in a critical review of the literature, reported 6 cases of congenital syphilitic aortitis in older children and added 1 case of his own, that of a boy aged 13, with confirmation of the diagnosis at autopsy. Of the 7 cases that he cited, 2 had been questioned by Stolkind at an earlier date. McDonald's [19] review of the literature embraced both the infantile and the late congenital syphilitic aortitis, and he reported 6 cases of congenital syphilitic aortitis confirmed by autopsy. The average age of the patients in this group was 14 years. One case of his own was added to this series, that of a boy aged 9, who had interstitial keratitis and a family history of syphilis. The postmortem examination revealed typical syphilitic aortitis and acute yellow atrophy of the liver, possibly due to the arsenic which the child had been receiving. McDonald later reported 11 more cases of syphilitic aortitis in young adults with confirmatory observations at autopsy.

Norris [20] reported 2 cases of congenital syphilitic aortitis. The patients were a 9 year old girl and a boy of 17 years. The gross and microscopic appearance of each aorta was typical of syphilitic aortitis. Each of the patients, like the 2 in McDonald's series, had met with sudden death.

Up to the present time we have been unable to find any report of a case of congenital syphilitic aortitis in an older child in which S. pallida was found. A possible explanation of the failure to demonstrate the spirochetes in the tissue of the aorta, as suggested by Morhardt [21] and by McDonald, is that such patients are allergic to the products of the spirochetes and that their aortitis is an expression of this allergy.

In the case of aortitis reported here four aneurysms were present in the ascending and transverse portions of the aorta. Waterman,[22] in 1908, suggested that infantile syphilitic mesaortitis may give rise to aneurysms later in life. Cases of aneurysmal formation in the older age group have been reported by von Zetkowsky,[23] Paul,[24] Nixon, Willson and Marcy [25] and Heiman.[26] In all cases except that reported by

18. Schulte, K.: Ztschr. f. Kreislaufforsch. **22**:753, 1930.

19. McDonald, S., Jr.: Brit. J. Ven. Dis. **10**:183, 1934.

20. Norris, R. F.: Bull. Johns Hopkins Hosp. **57**:206, 1935.

21. Morhardt, P. E.: Presse méd. **37**:340, 1929.

22. Waterman: Nederl. tijdschr. v. geneesk. **44**:832, 1908.

23. von Zetkowsky, 1916, cited by Stolkind.[16]

24. Paul, F.: Virchows Arch. f. path. Anat. **240**:59, 1923.

25. Willson, R. N., and Marcy, A.: Rupture of an Aortic Aneurism in a Child of Four Years, J. A. M. A. **49**:15 (July 6) 1907.

26. Heiman, H.: Arch. Pediat. **36**:543, 1919.

Willson and Marcy the condition was definitely diagnosed as congenital syphilis. Paul's patient had both a thoracic and an abdominal aortic aneurysm, the latter rupturing. The patient observed by Willson and Marcy, a child aged 4, died of a ruptured thoracic aneurysm. In this connection Norris suggests that in sudden death occurring in young persons syphilis should be considered as a possible etiologic factor.

SUMMARY

A case of productive aortitis with four thoracic aneurysms in an 11 year old girl is presented. Syphilitic causation is suggested, but no congenital stigma of syphilis was established.

Progress in Pediatrics

NEOPLASMS PRODUCING ENDOCRINE DISTURBANCES IN CHILDHOOD

ROBERT E. GROSS, M.D.
BOSTON

Occasionally my associates and I have been faced with the problem of making a preoperative or antemortem diagnosis for a child with an obvious endocrine disturbance which presumably has been caused by a new growth in one of the glands of internal secretion. In many instances the correct diagnosis has been obvious, while at other times considerable confusion has arisen among members of the staff regarding which gland was actually the seat of neoplastic disease. It therefore appeared desirable to me to review our material and to set forth herewith typical examples of clinical pictures which are produced by hormonologically active neoplasms of the testicle, ovary, adrenal gland, pineal body and hypothalamic region. The cases here presented do not include all of those which we have been privileged to study, but rather they have been selected so that each case is illustrative of a fairly well defined and easily recognized syndrome. Most of the experience here set forth has been derived from patients at the Children's Hospital of Boston, but a few additional illustrative cases have been included from the literature to make the survey more complete.

In the study of a given child with an endocrinologic abnormality, the clinician who attempts to make a diagnosis of the underlying condition must consider and possibly exclude numerous poorly understood aberrations which for want of a better term are grouped under the general heading of "polyglandular disturbance." Then, too, there is frequently the question of just what constitutes the normal state and whether the individual patient might be exhibiting a family or racial characteristic regarding the development of obesity, early appearance of puberty or exhibition of rapid skeletal growth. With these two problems—the polyglandular disturbances and the establishment of norms of development—the present work is not concerned. Instead, I have limited myself to listing the neoplastic diseases of the glands of internal secretion which might possibly be alleviated or cured by surgical procedures.

This publication was supported by a grant from the Godfrey M. Hyams Trust.

From the Department of Surgery and the Department of Pathology of the Children's Hospital, the Peter Bent Brigham Hospital and the Harvard Medical School.

GRANULOSA CELL CARCINOMA OF THE OVARY

Better known for its endocrinologic effects in postmenopausal life, when it brings about reestablishment of menstrual flow and hyperplasia of the breasts, the granulosa cell tumor of the ovary is also encountered in childhood and, indeed, in infancy. In 1935, Bland and Goldstein published an excellent treatise on cases of granulosa cell tumor which had been recorded in the literature previously. Of 150 cases in which the age of the patient was mentioned, they found that in 11 the patients

Endocrinologic Disturbances Produced by Neoplastic Diseases in Childhood

	Granulosa Cell Carcinoma of Ovary	Tumor of the Adrenal Cortex in Female	Tumor of the Adrenal Cortex in Male	Tumor of the Adrenal Medulla (Pheochromocytoma)	Tumor of the Third Ventricle in Female	Tumor of the Third Ventricle in Male	Pineal Tumor (in Male Only)
Masculinizing tendency (large clitoris or penis, deep voice, masculine contour)	0	++	+++	0	0	+++	+++
Feminizing tendency (breast and labial development)	+ to +++	0	0	0	+++	0	0
Precocious menstruation	+++	0	0	0	+++	0	0
Hypertension	0 to +	+ to ++	+ to ++	+++	+ to ++	+ to ++	0
Increased bone age (determined by roentgenograms of carpal bones and epiphyses)	0 to ++	+++	+++	0	+++	+++	+++
Acne	0	+++	+++	0	0	0	0
Genital hirsutism	+ to ++	+++	+++	0	+	+++	+++
Disturbance of water balance (oliguria or polyuria)	0	0	0	0	+++	+	0
Decrease or increase in blood cholesterol	0	+++	—	—	+	—	—
Increased excretion of estrogen in urine	+++	+++	+++	0	+ to ++	—	—
Increased excretion of androgen in urine	—	+++	+++	—	—	—	+++
Increased excretion of gonadotropic substance in urine	0	0	0	0	0	0	—

were children under 10 years of age (the youngest being 3½ years of age [1]) and that in 7 they were 10 to 14 years of age. In a female child or baby the triad of (1) enlarging mass in the lower part of the abdomen or the pelvis, (2) hypertrophy of the breasts, nipples or labia and (3) discharge of blood from the vagina forms a clinical picture which is almost unmistakably produced by a functioning ovarian neoplasm. The appearance of these symptoms in the order given is rather characteristic and suggests that the growth must be present for a considerable time before it produces estrogen in high enough concentration to bring about

1. In a personal communication, Dr. Clifford B. Lull, of Philadelphia, informs me that he has recently performed an operation in a case of granulosa cell tumor of the ovary in a 9 month old baby.

its remote effects on the external genitalia and the breasts. Furthermore, it indicates that the increased liberation of sex hormones must exist for a long time before menstrual flow begins, a fact which closely coincides with the finding of increased excretion of sex hormones in the normal female for many years before maturation takes place.

The changes in the breast are apt to be minimal and may be so slight that they are overlooked. In Bland and Goldstein's patient,

Fig. 1.—Photograph of 7 year old girl with granulosa cell carcinoma of the ovary. Note the advanced physical development, the enlargement of the breasts and the pubic hair (Bland and Goldstein).

however, there was marked enlargement of the breasts (fig. 1). This finding was similar to the change seen in elderly women with these tumors, fulness, tenseness and tingling of the breasts being common at that age. This suggests that in the child or infant direct stimulation by estrogen alone produces less hypertrophy than in the adult breast, which has possibly been sensitized or aided by hormones from the pituitary gland. In this regard, it is important to note that the changes of the breast in our patient with the granulosa cell tumor (case 1) were

far less than in the girl with a third ventricular lesion which was presumably acting via the pituitary body (case 7).

The growth of pubic hair is scanty, and while it is definitely more than normal, it amounted to so little in our case 1 that we were unable to get a satisfactory picture of it in a photograph. Other cases have been reported in which pubic air was abundant and axillary hair was also present.

Advancement of bony development, as roentgenologically demonstrated by early appearance of epiphyses or premature uniting of epiphyses, was not present in our cases but was said to be a marked feature in Bland and Goldstein's patient. It is not surprising to find these changes in the skeletal age, for Talbot demonstrated that injections of estradiol into immature rats caused a significant advance in the skeletal age of female animals, though not in that of male animals. Whether this stimulation of growth is brought about by direct action of estrogens on the bone or whether it is produced indirectly through enhanced pituitary activity has not been proved.

In this endocrine disorder there is an enormous production and excretion of estrogen, hence the most marked effects are seen in the uterus and the endometrium. The uterine body and cervix in our 13 month old baby were about twice the size expected for an infant of this age. This was determined by rectal examination prior to operation and was further confirmed by direct observation of the uterine body at pelvic laparotomy. Endometrial hyperplasia precedes the onset of menstruation.

The amount of uterine bleeding is variable. At first only a few drops of blood was passed daily per vaginam in our case 1, but later the flow became rather copious and the red blood count fell to 3,700,000 cells per cubic millimeter. These uterine discharges of blood may appear at irregular intervals and may be of serious amount. Such a process suggests that production of estrogen is unchecked by corpus luteum hormones. In other cases, however, the uterine bleeding assumes a cyclic character, appearing about once a month, lasting two to four days each time and having the characteristics of a precocious but otherwise normal menstrual flow.

With present day methods of determination of estrogen by quantitative colorimetric or animal assay, the laboratory offers considerable aid in establishing a correct diagnosis. The liberation of estrogen by granulosal neoplasms of the ovary may be detected by examination of samples of blood, but estimations made from twenty-four hour specimens of urine are adequate and are less disturbing to the patient. In the case here recorded, twenty-four hour specimens of urine contained a total of as much as 17,500 international units of estrogen. After operation this figure fell well below 50 units.

The determination of estrogen levels in the urine not only can be used as a diagnostic measure but possibly may be employed from time to time to detect the recurrence of a removed neoplasm before it has manifested itself clinically. It is certainly true that if a base line of excretion of estrogen has been established after operation and if there is a marked rise in excretion of estrogen as subsequent samples are studied, there is strong presumptive evidence of recurrence. However, it is difficult to state just how much of a rise in excretion of estrogen there must be postoperatively to ascertain whether recurrence has taken place. This is due to the fact that the normal daily excretion levels in childhood and infancy (Nathanson, Towne and Aub) have been only partially established. We were led astray by the check determination of estrogen in our case 1, in which an output of 48 units in twenty-four hours was shown. Falsely believing that this was well above normal, we thought that the baby had a recurrence, but when the abdomen was reopened no neoplasm could be found. Therefore, in the present state of knowledge, recurrence of the growth should be suspected only if the excretion of estrogen is undoubtedly above normal or if it rises above the base level which has been present since excision of the primary growth.

The reaction to the Ferguson test for excretion of gonadotropic substance is, of course, negative in these cases.

Granulosa cell tumors of the ovary show a great variety of histologic findings, ranging from a rapidly growing, highly malignant carcinoma in which the cells are massed in broad sheets to the more differentiated but less malignant form of so-called oophoroma or pfluegeroma, in which there are well developed cystic spaces lined by these cells and simulating follicle formation. The ovarian neoplasm in the case here reported contained an admixture of these types—some areas showing rapid growth while other zones were better differentiated and had formation of multiple cysts of varying size.

The excellent prognosis in these cases makes it important for the physician to recognize them and to advise surgical removal of the neoplasm before metastases have occurred.

CASE 1.—*Granulosa cell carcinoma of the ovary in a 13 month old child with presenting symptoms of precocious menstruation; oophorectomy and excision of ovarian tumor; child alive and without evidence of recurrence three years later.*

History.—C. M., a 13 month old white girl, appeared to be entirely normal until 5 months of age, at which time it was first noticed that the abdomen was protuberant and was progressively enlarging. Since the age of 5 months, the nipples and the external genitalia had shown slight but definite hypertrophy as compared with the normal size for infants of this age. On the day prior to hospitalization there had been a continuous vaginal discharge of small amounts of blood.

Physical Examination.—The child was well developed and well nourished and weighed 23 pounds (10,433 Gm.) (fig. 2). A single blood pressure reading was 134 mm. of mercury systolic and 70 diastolic. There was fine hair in the axillas, around the nipples and over the pubes, which appeared to be slightly but definitely more abundant than normal. The abdomen was protuberant, and the umbilicus was pouting. Within the abdominal cavity and lying somewhat to the right side there was a palpable mass about the size of a grapefruit. This elastic and non-tender structure filled the pelvis and extended well up above the umbilicus. The labia majora were slightly enlarged. A stringy blood clot was seen emerging from the vagina. Rectal examination disclosed an enlarged uterine cervix and uterine body.

Fig. 2 (case 1).—Postoperative photograph of a 13 month old girl with a granulosa cell tumor of the ovary. Note that there is no enlargement of the breasts. (The primary complaint had been vaginal bleeding.)

Laboratory Data.—Examination of a catheter specimen of urine gave negative results. The red blood count was 3,700,000 cells per cubic millimeter with 8 Gm. of hemoglobin per hundred cubic centimeters. Roentgenograms showed the skull, chest and long bones to be normal. There was no evidence of increased osseous growth. Intravenous pyelograms showed normal renal pelves and calices, but the right ureter was moderately enlarged and was displaced laterally. The content of cholesterol in the blood was 160 mg. per hundred cubic centimeters. The values for serum calcium and phosphorus were normal. A twenty-four hour specimen of urine contained 17,500 international units of estrogen.[2] The reaction to a Ferguson test for excretion of gonadotropic substance in the urine was negative.

2. This and all subsequent hormone assays noted in this paper were performed by Dr. Ira T. Nathanson.

Operation.—Laparotomy was performed on Nov. 12, 1936 with the patient under ether anesthesia. A large, mottled-appearing, rounded mass was found rising from the right ovary. It was not adherent to the neighboring structures. This growth was partially solid and partially cystic and possessed an unbroken, highly vascular capsule. There were no metastases to regional lymph nodes or to other abdominal viscera. The neoplasm, the flattened remaining portion of ovary, the right uterine tube and a large wedge of the broad ligament were removed. The uterus, which was about twice its normal size, was suspended satisfactorily, and the abdomen was closed.

Pathologic Examination.—The tumor measured 11.5 by 15 by 12 cm. It consisted of a partially solid and partially cystic structure (fig. 3). The surface was smooth, moist, glistening and slightly lobulated, but there were no papillary projections from the outer surface to suggest extension of the neoplasm beyond the capsule. However, one part of the capsule had been torn during removal of the mass from the abdominal cavity, at which time about 750 cc. of clear, amber-colored fluid had escaped. When the specimen was cut open it was apparent that about

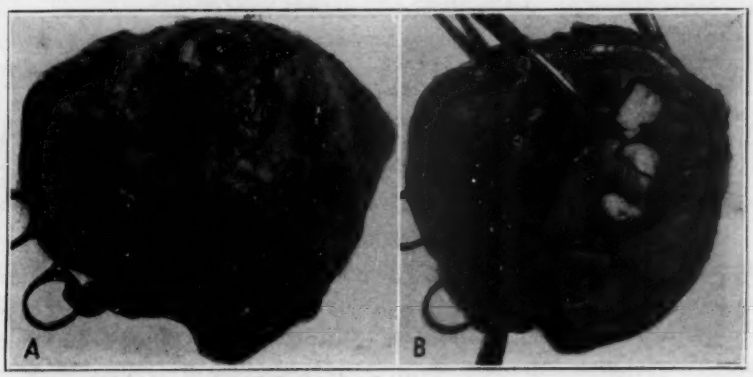

Fig. 3 (case 1).—Surgical specimen, granulosa cell neoplasm of the ovary. *A*, cross section of the solid portions of the mass. *B*, cystic portion opened to show the internal pedunculated growth.

one third of its volume had been composed of solid tissue and about two thirds had been cystic. Projecting into the cyst cavity were multiple nodules of tumor tissue varying from 1 to 3 cm. in diameter. These varied from gray to yellow-gray and were soft. Some of them were attached to the wall by a broad base, while others were pedunculated. The main portion of the solid tumor tissue was likewise soft and gray or yellowish, and it had the appearance of a highly cellular growth. The fluid from the tumor assayed 3,000 international units of estrogen per liter.

Microscopic examination showed an epithelial neoplasm which was very cellular and which possessed little supportive stroma. In some fields there were broad sheets of cells with evidence of rapid growth. Elsewhere there was a less malignant appearance, and the cells were arranged in round small cystic spaces but not in any layered arrangement to suggest the formation of a theca interna and theca externa of a normal ovary. The cells were usually rounded or oval but in some places were fusiform. There was moderate variation in cell size. The cell borders were well defined, and the cytoplasms stained poorly. The nuclei varied considerably

in chromatin content. Mitotic figures were rarely seen in some areas, but in other places there were as many as five to ten in a high dry field. The vascularity was rather low, and there were many small areas of tumor necrosis. The findings were typical of a granulosal cell carcinoma of the ovary.

Postoperative Course.—After operation the convalescence was satisfactory, and the child was discharged on the fifteenth postoperative day. Small amounts of blood were passed per vaginam for the first fourteen postoperative days, but after this period there was no further bleeding.

On April 14, 1937, a specimen of twenty-four hour urine contained 48 international units of estrogen. The breasts and the labia pudendi had regressed almost to normal size, and the previously noted fine hair of the pubes and axillas had disappeared. The red cell count and the hemoglobin were normal. The blood pressure had returned to normal levels, ranging from 100 mm. systolic and 50 mm. diastolic to 110 mm. systolic and 60 mm. diastolic. In spite of the fact that there was no evidence of recurrence by physical examination, it was felt that the relatively high excretion of estrogen for a child of this age probably resulted from recurrence of the neoplasm. Pelvic exploration was therefore advised and undertaken, but no recurrence was found. The uterus had returned to normal size.

The subsequent course of this child has been satisfactory during the three years since removal of the tumor. There have been no symptoms or signs of recurrence of the neoplasm. There has been no return of the vaginal bleeding. Examinations of twenty-four hour specimens of urine showed a total estrogen excretion of 30 international units on May 3, 1937.

ARRHENOBLASTOMA OF THE OVARY

In recent years considerable attention has been directed toward the arrhenoblastoma of the ovary, a neoplasm which causes regression of the secondary female characteristics, with cessation of menstruation, atrophy of the breasts, and loss of feminine bodily contour, and subsequent development of male features, including a deepening voice and growth of beard. The importance of recognizing these growths lies in the fact that after removal of the neoplasm there is a loss of the male features and a resumption of the female characteristics. Novak (1936; with Gray, 1938) has made an excellent presentation of the condition as it occurs in adult life, summarizing the findings in 51 cases, including 6 of his own.

This growth is primarily one of young adult life, occurring chiefly in the age group from 20 to 30 years. The youngest patient found mentioned in the literature was a girl 15 years of age. Since the condition does not appear in the age group being considered in this presentation, arrhenoblastoma of the ovary will not be further considered.

TESTICULAR NEOPLASMS WITH PRECOCIOUS SEXUAL AND BODILY DEVELOPMENT

Neoplasms of the testicle, arising from the interstitial cells, may produce a striking precocity in the preadolescent boy. While these tumors are more common in adult life, at least two reports have been

made describing amazing precociousness in boys. Rowlands, Nicholson and Parkes Weber studied a patient 9 years of age who had a swelling of the left testicle, with premature puberty. Up to the age of 6 years, nothing abnormal had been noticed. Then the boy grew with great rapidity; his voice "broke" at 7 and at 8 years he attained puberty.

On admission to the hospital, the patient appeared to be an almost fully grown man of about 18 years of age, being 5 feet (152 cm.) tall, powerfully built and with much hair on his chest, loins and pubis. His intelligence was above the average for his age. The right testicle was of normal size for a boy of 9 years, but the left one was about five times as large, owing to an elastic globular tumor in the body of the testis. The penis was fully developed.

The left testicle and its neoplasm were removed, and the histologic examination was reported to show a growth which was presumably derived from the interstitial cells of the testis. It is interesting to note, however, that the cytoplasm of many of the cells stained deeply with eosin—a characteristic which was noted in the growth removed from the patient in our case 2, who had a carcinoma of the adrenal cortex. This raises the possibility of neoplasms arising in adrenal rests, which are found fairly frequently along the inguinal canal or in the epididymis. Rowlands and his associates refer to a 9½ year old patient of Sacchi who likewise had an amazing muscular and sexual development and a heavy growth of beard associated with a testicular tumor.

NEOPLASMS OF THE ADRENAL CORTEX WITH SYMPTOMS OF MASCULINIZATION

Except for rare instances in which carcinoma of the adrenal cortex produces a picture similar to hypophysial basophilism, it is usually characteristic for cortical neoplasms to bring about striking changes of masculinization in both girls and boys. Although the masculinizing features are the symptoms which call the condition to the parents' attention, there are other important changes which help complete this well defined syndrome.

The neoplasm may or may not be found by abdominal palpation. More often than not, the growth can be felt through the thin abdominal wall of a child, but in some cases—even after several years of symptoms—the mass may still be small enough to elude detection by physical examination.

Roentgen examination of the abdomen may be of some help. In case 2, a faint, rounded, golf ball–sized shadow was seen just above the right kidney, but one is usually not fortunate in seeing the tumor outlined as easily as this.

Intravenous or retrograde pyelography usually shows no distortion of the renal pelves, but if the adrenal mass is large enough one or the other kidney will be displaced downward. Pyelographic examination should be performed in all cases, for if at operation it is decided to remove the kidney along with the adrenal tumor, it is well to have determined beforehand that a kidney is present on the opposite side.

It has been obvious for years that many of the clinical changes in patients with neoplasms of the adrenal cortex have been produced or accelerated by an increased liberation of androgen, but only recently have we had direct evidence from the laboratory that a quantitative increase in this hormone can actually be demonstrated. While there is still some confusion concerning the standardization of colorimetric methods of measuring this substance and correlating the values thus obtained with animal assay methods, it is still an undisputed fact that such studies always show an enormous excretion of androgen in the urine. These findings are strikingly illustrated in the patient in case 2, a girl of 3 years, in whom the normal excretion in a twenty-four hour period should not be over 8 to 10 international units of androgen. To our amazement, the excretion levels in this child rose as high as 300 units in twenty-four hours, and the figure fell to normal within ten days after removal of an encapsulated adrenal neoplasm. In those communities or hospitals where facilities are present for making such studies, the redetermination of the urinary excretion of androgen from time to time may give valuable and possibly initial evidence of recurrence of a previously excised malignant adrenal growth.

Frank has reported the finding of large amounts of estrogenic substance in the urine of 4 patients who had adrenal cortical carcinomas. He concluded that apparently "adrenal cortical carcinoma alone of adrenal tumors increases the amount of estrogenic substance in the urine to as high as from 1,000 to 10,000 mouse units per liter, with a negative pregnancy test." However, cases of adrenal cortical neoplasm have been reported in which this test was negative. In short, it probably summarizes the present state of knowledge to say that the finding of large amounts of urinary estrogenic substance (in the absence of a positive test for pregnancy) is highly suggestive of a cortical adrenal neoplasm, but that negative results do not rule out such a neoplasm.

In the female the clinical findings are well typified by our case 2, in which most of the aberrations about to be listed were present. The enlargement of the clitoris is an almost constant finding. The organ becomes several times its normal size and may be 2 or 3 cm. in length. Its diameter is increased, and its consistency is firmer. The labia minora folding around the structure give it an appearance closely simulating a

small penis in size and contour (fig. 4). In some cases the clitoris hypertrophies to such an extent that encroachment on the external urethral meatus causes partial obstruction to the flow of urine.

With the enlargement of the clitoris, pubic hair appears in abundance. This hair is long, coarse and usually dense. It does not always have a "male distribution," that is, extending upward in a triangular shape toward the umbilicus. Indeed, it is more likely to be limited to the

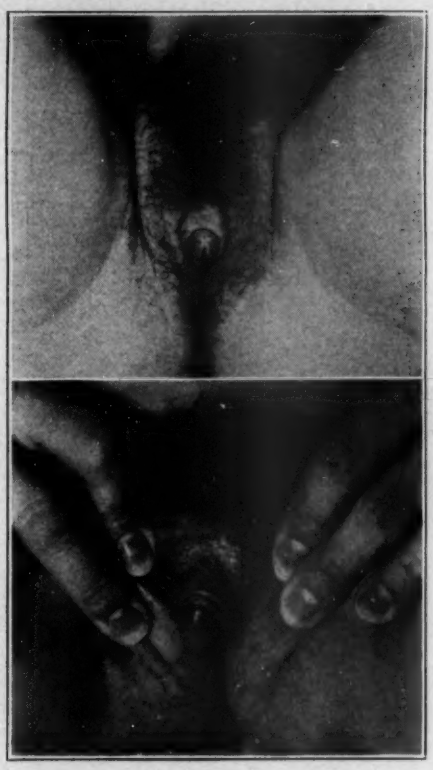

Fig. 4 (case 2).—Marked growth of pubic hair and hypertrophy of clitoris and labia in a 3 year old girl with masculinizing neoplasm of the adrenal cortex.

pubis itself (fig. 5). Such changes in the genitalia and in appearance of pubic hair may be seen at a very early age, and in case 2 the patient's mother noticed these abnormalities in the second week of life.

Secondary sexual changes are manifested particularly by changes in the voice, and a child who previously spoke in a normal fashion will now have a voice which is alternately high pitched and deep, like that of a youth whose voice is "changing" at puberty. In a case in which the condition is fully advanced the voice is permanently low pitched and has a husky quality.

The musculature and skeletal frame of a girl with this condition show a decided change toward the male type (fig. 5), with increase in the size and firmness of the muscles of the trunk and extremities, squaring of the hips and shoulders and a stocky appearance to the wrists, hands and neck. The bony framework is obviously more massive than normal. The feminine contour is partially or completely lost, and the habitus is strikingly that of a powerfully built boy of an older age.

Roentgenographic examination of such a child discloses a great advancement in the bone age when observations are made on the development of epiphyses, the fusion of epiphyses and the number of carpal bones

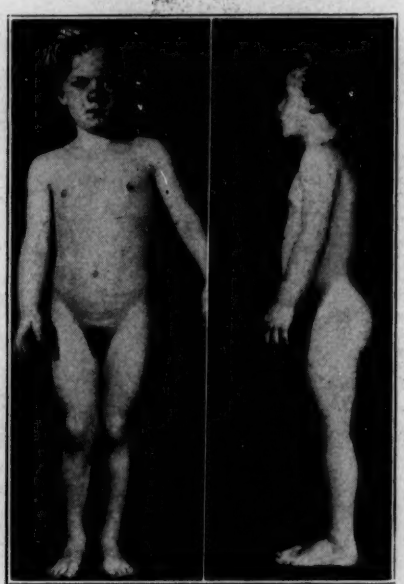

Fig. 5 (case 2).—A 3 year old girl with adrenal cortical neoplasm. Note the masculine appearance, squared shoulders, muscular build, large hands and pubic hair.

which are calcified (fig. 6). Advancements in bone age of two to four years are common. We have not made roentgenologic studies in all our cases of adrenal cortical neoplasms, but when such studies were made there was always indisputable evidence of an osseous advancement in patients with masculinization.

There is some evidence that a disturbance in cholesterol metabolism may be brought about by adrenal cortical tumors. It is not known how frequently blood cholesterol levels are altered, because observations on this point are not numerous. However, 2 of our patients showed definite abnormalities in the blood levels of this substance. In 1 case the total cholesterol was elevated, while in case 2 it was depressed to

the unusually low figure of 38 to 52 mg. per hundred cubic centimeters. A further study of the blood fats in this case disclosed the level of free cholesterol to be 23 mg. per hundred cubic centimeters and the cholesterol esters to total 24 mg.

Hypertension is described as a common finding in adrenal cortical tumors, and it has been our experience that some elevation of the systolic level is seen in nearly all cases. In 1 instance the systolic pressure was as high as 190 mm. of mercury, but in other patients it was not recorded at any time to be above 130 or 140 mm.

Papular eruptions on the skin, similar to a form commonly encountered in the normal adolescent youth, are often found. They are apparently produced by excessive secretion of androgen. While it is

Fig. 6 (case 2).—Roentgenogram of the hand of a 3 year old girl with adrenal cortical neoplasm at the left, compared with that of a normal girl of the same age at the right, showing the patient's advancement in bone age.

not observed in all cases, its presence in a child with an endocrinologic disturbance greatly aids the physician in making a correct diagnosis. If present, these cutaneous changes are most prominent on the face and forehead (figs. 7 and 8), but they are also found on the shoulders, the upper part of the back and the chest above the nipples. The relation of these cutaneous lesions to a hormonal imbalance is suggested by the disappearance of the acne in cases in which it was possible to remove the adrenal growth completely.

In addition to physical precocity, an advance in mental development may be found in some cases. One of our patients was several years ahead of expected development, as judged by the school subjects which

Fig. 7 (case 2).—Masculinizing adrenal cortical neoplasm in a 3 year old girl, with acne of the face, noted particularly on the forehead, cheeks and chin.

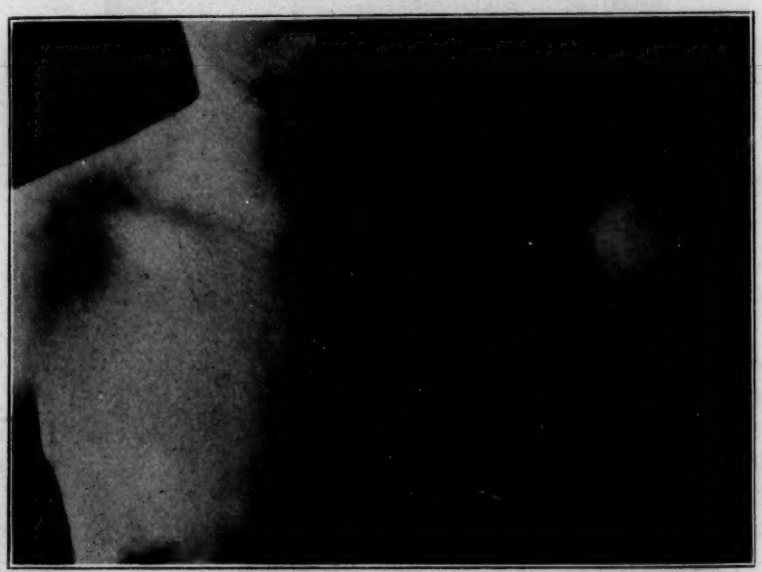

Fig. 8 (case 2).—Acne of thoracic skin in patient with tumor of the adrenal cortex.

had been mastered. However, on 2 other patients with known adrenal cortical neoplasms, we have had psychometric tests performed without finding any particular aptitude or elevation of the intelligence quotient.

In the male the changes already enumerated are likewise found, including deepening of the voice, overdevelopment of the skeletal musculature, hypertension, acne and roentgenologic evidence of increased bone growth. In addition, the accentuation of primary male sexual characteristics is a striking feature, and the penis and testicles may approach adult size many years before puberty. Such extraordinary development of the genitalia may be seen even in the early years of life and is well illustrated in the boy of 3 years shown in figure 10. The growth of genital hair may be abundant.

CASE 2.—*Tumor of the adrenal cortex in a girl 3¼ years of age, with masculinization, enlarged clitoris, growth of pubic hair, deep voice, acne, boyish contour and hypertension; high urinary excretion of androgens; removal of encapsulated adrenal neoplasm followed by abatement of sexual aberrations.*

History.—C. S., was a girl 3 years and 3 months old whose chief complaint was enlargement of the clitoris and difficulty in urinating. The birth and subsequent development with regard to sitting, standing and gain in weight were normal for the first year of life. When the mother had first inspected the child, on the twelfth day of life, she had noticed that there were an undue prominence of the anterior portion of the vulva and a few pubic hairs about ½ inch (1.27 cm.) in length. During the first year of life the clitoris progressively increased in size. During the second year the distal portion of the clitoris particularly developed, so that a prominent "head" was noted. During the third year of life the clitoris reached its largest dimensions and protruded between the labia majora. During these three years there was a steady increase in the length and amount of the pubic hair.

When the child started to talk, at the age of 13 months, it was noticed that her voice was unusually deep, and this quality continued unchanged thereafter. During the second and third years of life there was a great development in size and strength, until at the time of hospitalization she was larger and stronger than her 5 year old sister, who was considered to be normal. She had a voracious appetite. Since the age of 3 months there had been a definite acne of the face, upper part of the chest and back, which had not grown worse with increasing age.

Physical Examination.—The child was exceedingly well developed and had a distinctly masculine contour, with wide shoulders and a broad, sturdy back (fig. 5). The hands were thick and square, with stubby fingers. The skin was thicker than that of a normal girl. There was a relatively small amount of subcutaneous fat. The musculature of the back, trunk and extremities was exceedingly well developed, had an excellent tone and felt like that of an athletic type of boy several years older. She was obviously much larger than would be expected for a girl of her age. The circumference of the head was 20¾ inches (53 cm.); the height, 42 inches (107 cm.), and the span between the finger tips of the abducted and outstretched hands, 41 inches (104 cm.). Her weight was 45 pounds (20.4 Kg.). Her voice was as low pitched as that of an adolescent male. The skin of the forehead, and cheeks, chin, the upper part of the chest and the back between the scapulas was shiny, greasy and covered with multiple small acneform lesions (figs. 7 and 8). The breasts were not enlarged. There was an abundant growth of pubic hair, with

feminine distribution. The labia majora were larger than normal, and protruding between them was a much enlarged clitoris about 1½ inches (3.8 cm.) long (fig. 4). The glans of the clitoris was ⅜ inch (0.96 cm.) in length and in diameter, the labia minora forming a fold somewhat resembling the foreskin of a male. There was a moderate amount of perianal hair. The blood pressure was 116 mm. of mercury systolic and 50 mm. of mercury diastolic. No abnormal masses could be felt in the abdomen or flanks.

Laboratory Data.—The urine was normal. The red cell count was 5,200,000 cells per cubic millimeter. The white cell count was 10,400 cells per cubic millimeter. There was 85 per cent hemoglobin. The nonprotein nitrogen level was 33 mg. per hundred cubic centimeters. The chloride content of the blood was 106 milliequivalents per liter; the potassium content, 6.4 milliequivalents per liter; the sodium content, 141 milliequivalents per liter; the calcium content, 10.6 mg. per hundred cubic centimeters; the phosphorus content 5.6 mg. per hundred cubic centimeters; the phosphatase content, 11.8 Bodansky units per hundred cubic centimeters; the serum protein content, 7.5 mg. per hundred cubic centimeters. The cholesterol content varied from 38 to 47 to 58 mg. per hundred cubic centimeters on three determinations; further examination of the specimen showing a cholesterol level of 47 mg. gave values for free cholesterol of 23 mg., and for cholesterol esters of 24 mg. The results of a sugar tolerance test were as follows: fasting level 98 mg. per hundred cubic centimeters; level one-half hour after ingestion of dextrose, 250 mg.; one hour, 182 mg.; two hours, 161 mg.; three hours, 75 mg. A smear made from the vaginal wall showed no cornified epithelial cells. Examination of a twenty-four hour specimen of urine showed an excretion of 370 mg. of creatine. Examinations of twenty-four hour specimens of urine on four different days showed the following excretions of estrogen and androgen:

Specimen	Androgen, International Units	Estrogen, International Units
1	424	1,296
2	296	10,120
3	240	7,776
4	1,120	540

Roentgenographic examination of the skull gave negative results; the sella turcica was normal in size. Films of the hands and feet showed the osseous development to correspond with that of a child 9 or 10 years old (fig. 6). All the bones were large and heavy, and the phalanges and metacarpals were short and thick. A film of the abdomen showed what appeared to be a rounded mass about 6 cm. in diameter just beneath the liver and overlying the upper pole of the right kidney. Intravenous pyelograms showed normal conditions except for slight downward displacement of the entire right kidney. The basal metabolic rate was + 7 per cent by weight, + 15 per cent by height and — 3 per cent by urinary excretion of creatinine.

Course and Operation.—The daily blood pressure readings varied from a low of 98 systolic and 54 diastolic to a high of 130 systolic and 80 diastolic, averaging around 110 systolic and 70 diastolic. With the patient under ether anesthesia the right renal fossa was explored extraperitoneally. Lying above the kidney and replacing the adrenal gland was a well encapsulated, rounded, mottled, orange-colored neoplasm about 5.5 cm. in diameter. The tumor was easily dissected away

from surrounding structures by blunt dissection. Several large blood vessels entered the neoplasm, at least one of these communicating directly with the vena cava.

Pathologic Examination.—The gross specimen weighed 110 Gm. and measured 7.5 by 6.5 by 4 cm. It was well encapsulated, was smoothly rounded (fig. 9) and had a distinct orange color. It was elastic and rather soft. Numerous large blood vessels coursed over its surface. The cut section showed the mass to be solid. The tissue varied from a golden brown to brownish gray, was soft and had a cellular appearance. There was good preservation, and no areas of necrosis were seen in the gross examination.

Microscopically, the lesion was an adrenal cortical carcinoma. The cells appeared in broad sheets in a purposeless arrangement, with only a scanty reticular stroma. The cells varied greatly in shape, and many of them were extremely

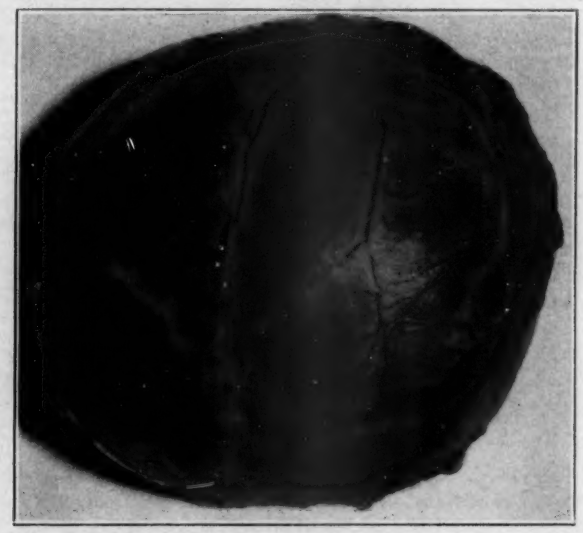

Fig. 9 (case 2).—Encapsulated adrenal cortical neoplasm from a 3 year old girl. The maximum cross dimension was 7.5 cm. The growth had a distinct orange color.

large. An unusual feature was the appearance of the cytoplasm of many cells, which stained a deep pink in the hematoxylin and eosin preparations and a homogeneous blue in phosphotungstic acid hematoxylin sections. This quality of the cytoplasms suggested the possible relation of these cells to those of the normal fetal adrenal cortex. The nuclei varied greatly in size and shape and possessed a delicate, lacy-appearing chromatin network, and some of them contained a prominent nucleolus. Most cells had but one nucleus, but others contained three or four. Mitotic figures were not numerous, but atypical forms were encountered. The pathologic diagnosis was malignant tumor of the persistent fetal cortex of the adrenal.

Postoperative Course.—Following operation the child made an uneventful recovery except for marked abdominal distention during the first two days. After the fourth postoperative day the highest blood pressure recorded was 114 systolic and 60 diastolic.

Chemical studies of the blood performed on the ninth postoperative day showed a slight and probably insignificant fall in the chloride content to 100 milliequivalents per liter, and in the sodium content, to 133 milliequivalents per liter, while the cholesterol content had risen to 113 mg. per hundred cubic centimeters. Postoperative examinations of specimens of twenty-four hour urine for androgen and estrogen gave the following values:

Postoperative Day	Androgen, International Units	Estrogen, International Units
2d	12.0	18
6th	15.5	24
8th	10.6	288
10th	8.0	10
14th	4.3	8

Within two months after removal of the neoplasm, the cutaneous lesions had entirely disappeared, the "great strength" had markedly diminished, the excessive appetite had disappeared and the clitoris was considerably shrunken. When the

Fig. 10 (case 3).—A 3 year old boy with a large, malignant neoplasm of the left adrenal gland. The penciled line on the abdomen indicates the outline of the growth. Note the pubic hair and the greatly enlarged genitalia.

patient was last seen, eight months after operation, the pubic hair had not yet changed; the voice was still somewhat husky, but the child was becoming more feminine in appearance and actions.

CASE 3.—*Malignant neoplasm of the adrenal cortex in a 3 year old boy with marked sexual precocity and increased bone age; operation for adrenal tumor on the left side; death.*

History.—L. C. was a 3 year old boy who had been entirely normal until four months previous to admission, when it was first noticed that he was overdeveloped mentally and physically. His mannerisms were thought to be those of a boy several years his senior. During this four month period there were marked changes in his physical makeup. The genitalia had greatly increased in size, the body weight had increased, pubic and mammary hair had appeared, and the voice had become deep and mature. During the two months before admission, the musculature of the arms and legs showed progressive weakness and the child became fatigued easily. For one month there had been attacks of intermittent abdominal pain, and during this time there had been a noticeable increase in size of the abdomen.

Physical Examination.—The patient was quite large and possessed the stature of a child 6 or 7 years old (fig. 10). He acted like a boy much older than his stated age of 3 years. The skin was sallow in appearance. The voice had a deep and coarse vibrant tone. On the areolas of the breasts were many fine hairs. The genitalia were greatly hypertrophied. The testicles and the penis were fully the size of those of an adolescent youth. Pubic hair was abundant, long, dark and coarse. There had been obvious wasting of the soft tissues of the extremities (presumably related to the advanced stage of his neoplastic disease). The abdomen was asymmetrically distended by a large (grapefruit-sized) mass which filled the left upper quadrant. This mass bulged in the loin and flared out the costal margin. It was firm, nontender and fixed. The left lobe of the liver appeared to be displaced medially forward and downward, so as to present in the epigastrium medial

Fig. 11 (case 3).—Roentgenogram (left) from patient with carcinoma of the adrenal cortex, compared with roentgenogram (right) from a normal boy of the same age.

to the previously described mass. The abdominal distention was sufficient to cause moderate respiratory distress.

Laboratory Data.—The urine was normal. Blood count showed: 4,550,000 red cells per cubic millimeter and 13,000 white cells. The blood nonprotein nitrogen was 17.4 mg. per hundred cubic centimeters. The test for renal function showed an excretion of 70 per cent of phenolsulfonphthalein in two hours. Roentgenograms of the abdomen showed a large soft tissue mass filling the left side and projecting beyond the midline toward the right. There were no metastases in the long bones or the chest. Roentgenograms of the carpal bones showed that the number of carpal bones ossified and the configuration of the bones was consistent with a skeletal development of a child of 6 or 7 years. No studies were made on the hormonal excretion in the urine.

Course.—With a preoperative diagnosis of adrenal cortex neoplasm, exploration was undertaken by a transabdominal approach. An extremely vascular tumor was found in the left renal fossa which extended from the diaphragm below the level of the umbilicus. It was believed impossible to remove this, but in view of the hopeless prognosis, enucleation was nevertheless attempted. During the process of removal the neoplasm ruptured, and ensuing hemorrhage could be controlled only with a pack. One end of the pack was brought out through the abdominal wall, which was rapidly closed. The child died in shock two hours later.

Pathologic Examination.—The specimen consisted of a mass of necrotic, pinkish yellow, lobulated material weighing 640 Gm. Surrounding a portion of the tumor was a thin, translucent membrane, but elsewhere there was no covering to the friable and highly cellular neoplasm. A few of the better preserved areas were yellowish, soft and fairly well preserved, but elsewhere there was extensive hemorrhage and the degenerating material had the consistency of a gruel. What remained of the compressed adrenal gland could be identified at one edge of the specimen.

Microscopically, the findings were those of a rapidly growing epithelial tumor of the adrenal cortex type. There was extreme variation in the histologic picture. In places the cells were rather uniform in appearance; they were cuboidal or multiangulated and had deeply eosinophilic cytoplasms and small, spherical and centrally placed nuclei. In such areas mitotic figures were rare, and the general arrangement of cells in small masses or trabeculae supported by a delicate stroma and lying between thin-walled blood vessels imparted an appearance reminiscent of normal adrenal cortex. However, the predominating fields showed a much more malignant growth, with cells of great variation in size and shape, some of which contained eight to ten nuclei, and numerous mitoses which were frequently multipolar. Here, the cells appeared in broad sheets, without purposeful arrangements, the vascularity was less, and necroses were common.

CARCINOMA OF THE ADRENAL CORTEX WITH A SYNDROME SIMILAR TO PITUITARY BASOPHILISM

Most of the carcinomas of the adrenal cortex in childhood produce a syndrome such as is described in the preceding section and conform to type sufficiently to justify setting them apart as an entity. However, it is becoming increasingly apparent that there are occasional adrenal cortical growths which produce a somewhat different clinical picture, which tends to be more like the syndrome of pituitary basophilism. These growths appear to be much more common in female subjects. Two patients (cases 4 and 5) whom we have observed are illustrative examples.

These children have no symptoms of masculinization—change of body contour or of muscular development, deepening of the voice or change in the genitalia. They tend to have a plethoric appearance, with increased deposition of fat over the body and face (figs. 12, 13, 14 and 15), though this change is not quite so striking as that described in cases of outspoken basophilism. Lethargy and weakness are fairly prominent. Hypertension is the outstanding finding. In our 3 year old patient this was observed to be as high as 190 mm. of mercury systolic

Fig. 12 (case 4).—A 10 year old girl with an adrenal cortical neoplasm who showed no signs of masculinization but whose symptoms were suggestive of pituitary basophilism.

Fig. 13 (case 4).—Same patient as in figure 12, showing the plethoric appearance of the face, the drowsy appearance of the eyes and the acne around the mouth.

Fig. 14 (case 5).—A 3 year old girl with some findings suggestive of basophilism. Note the obesity and the cretinoid appearance of the face and eyes. A neoplasm of the adrenal cortex was found at autopsy.

Fig. 15 (case 5).—A 3 year old girl with adrenal cortical neoplasm with some symptoms suggesting basophilism. *A*, showing lethargic appearance and marked obesity. *B*, photograph of the patient before onset of the present illness.

and 170 mm. diastolic, with a terminal rise to 260 systolic and 190 diastolic. There may be other phenomena secondary to such hypertension, such as excretion of urinary casts, evidence of cardiac failure, headache or cerebral vascular accident. One of these patients had mild acne of the facial skin.

A case which was somewhat similar to case 4 but in which the patient was older was reported by Graef, Bunim and Rottino. This patient, a girl of 19 years, had progressive weakness, increasing adiposity, swelling of the face and abdomen, marked striae atrophicae of the breasts, abdomen and extremities, excess hair on the face and slight hypertension. "The urine contained as much as 5,000 international units of estrogenic substance per liter, a quantity far exceeding that found in pregnancy. A control Friedman test for pregnancy was negative." No analysis was made for androgenic substances. At autopsy a large metastasizing neoplasm of the right adrenal gland and an indeterminate adenoma of the anterior lobe of the pituitary gland were found. We must regard the adrenal neoplasm in this case as being the exciting cause of the hormonal abnormalities and consider that the hypophysial adenoma was an incidental finding or else was produced secondarily by the adrenal neoplasm. That the latter explanation is the correct one is suggested by the work of Close, who found pituitary adenomas (either chromophobe or acidophilic) in 44 per cent of cases of carcinoma of various organs, whereas among other routine autopsy cases such adenomas were found in only 10 per cent.

Cases of this sort form an indefinite group which needs further study. By pathologic examination we cannot differentiate them from the cases in which there is evidence of masculinization. However, it is necessary to set them apart for two reasons: first, to point out a possible cause of hypertension in a juvenile patient—in the absence of nephritis; secondly, to draw attention to them and set them apart from cases of pituitary basophilism, which they resemble in several ways. This is important, for it is a grave clinical mistake to attempt to treat such a patient by roentgen irradiation of the pituitary gland while it is still possible to excise an adrenal growth before it metastasizes.

It might be quite difficult to make a differential diagnosis clinically between these cases and cases of pituitary basophilism. Certainly, if there has been any abdominal pain, as in case 4, or if there is a palpable mass in the upper part of the abdomen, the adrenal glands are more likely to be the seat of the primary disturbance. When there is reasonable doubt, pyelography by the intravenous or the retrograde route should be performed. Hormonologic studies may be of some aid in the future, but our present data give us little help in this regard. The experience of Graef, Bunim and Rottino suggests that in cases with

the primary trouble in the adrenal gland there will be a high urinary output of estrogenic substance, in contrast to basophilism, in which the excretion of gonadotropic substance should predominate. Further study along this line will very likely produce valuable diagnostic aids. If the differentiation must be made in a child, the chances are much in favor of an adrenal disturbance, because of the great rarity of pituitary basophilism below the age of 12 years.

CASE 4.—*Carcinoma of adrenal cortex origin, with a syndrome suggesting pituitary basophilism; 10 year old girl with swelling of the face, abdominal pain, acne of the face, hypertension, hyperglycemia, glycosuria, hypercholesteremia and diabetes mellitus; death from pneumonia.*

History.—M. L. was a white girl 10 years and 7 months old who had been entirely normal in development and activity until three months prior to hospitalization. For three months she had noticed increasing swelling of the face, shininess of the facial skin, onset of lethargy, easy fatigue, irritability and nocturia, with urination three to four times per night. For two months there had been a gradually increasing swelling of the abdomen, almost daily headaches and nocturnal pain in the abdomen and left hip. For one month there had been a facial rash.

Physical Examination.—The patient was a well developed and well nourished girl who did not appear to be acutely ill (fig. 12). She was somewhat apathetic but was cooperative. The face was reddened and shiny and had a plethoric, puffy appearance (fig. 12). The skin of the body and extremities was dry, rough and warm. There was a fine maculopapular rash on the face, particularly over the glabella and around the nose and the mouth. There were numerous hairs on the upper lip. The optic fundi showed some thickening of the retinal vessels. The heart was definitely enlarged. The heart beat was distinctly increased in force. The blood pressure was 160 mm. of mercury systolic and 120 mm. diastolic. The abdomen was somewhat distended, but no abnormal masses could be felt. The genitalia did not appear abnormal except for the presence of a few pubic hairs, which were light brown and rather straight.

Laboratory Data.—Five urine specimens showed specific gravity varying from 1.005 to 1.020; two showed a very slight trace of albumin; one contained rare granular casts, and all contained large amounts of sugar. The blood count showed 4,400,000 red cells per cubic millimeter, 11,800 white cells and 80 per cent hemoglobin; the smear was normal. The total blood protein was 6.2 Gm. per hundred cubic centimeters; the nonprotein nitrogen, 19 mg. The phenolsulfonphthalein excretion (intramuscular method) was 55 per cent in two hours. The blood calcium was 8.9 mg. per hundred cubic centimeters and the blood phosphorus, 4.2 mg. A dextrose tolerance test showed a fasting level of 190 mg. per hundred cubic centimeters and the following levels after ingestion of dextrose: in one-half hour, 266 mg.; in one hour, 278 mg.; in two hours, 312 mg., and in three hours, 186 mg. The cholesterol content was 340 mg. The spinal fluid showed normal dynamics and normal chemistry except for increased sugar. Roentgenograms showed slight cardiac enlargement and no pathologic cranial conditions. Films were not taken of the carpal bones or of the extremities.

Course.—The patient was in the hospital seven days preceding her death. For the first six days the temperature was normal, and she appeared in fairly good health, except for moderate lethargy. The blood pressure ranged from 138 to 148 mm. of mercury systolic and 90 to 120 mm. of mercury diastolic. On the sixth

day she had thirteen convulsive seizures, during which time her blood pressure was elevated to as high as 230 mm. of mercury systolic. The convulsions were thought to be due to cerebral vascular spasm associated with hypertensive crises. During the last twenty-four hours of life there was an increasing fever, the temperature reaching a level of 109.6 F. just prior to death.

Pathologic Findings.—Complete autopsy was performed eight hours after death. The general features of the external examination were the same as those noted during life. The thymus weighed 5 Gm. The heart weighed 160 Gm. (normal for the age, 116 Gm.). The kidneys were normal in size and shape, but the right one was displaced downward and outward by a neoplasm of the right adrenal gland. The right adrenal was largely replaced by a large, irregular mass, 10 by 11 by 9 mm. (fig. 16), which had extended over between the two kidneys and had displaced the pancreas forward. The growth had, therefore, surrounded and

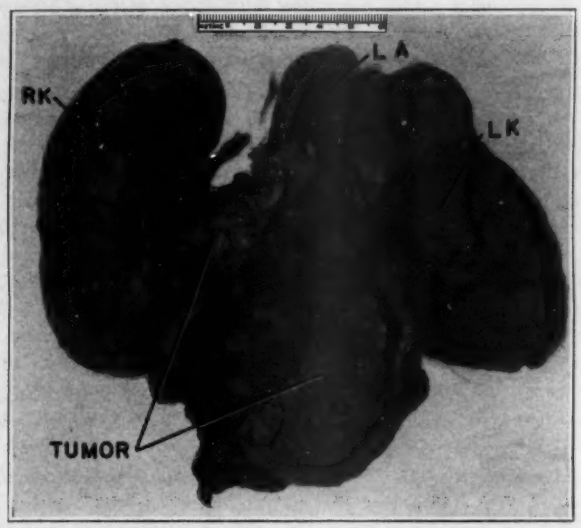

Fig. 16 (case 4).—Specimen from a 10 year old girl with findings suggestive of basophilism but with discovery at autopsy of a carcinoma of the right adrenal gland. *LA,* left adrenal; *LK,* left kidney; *RK,* right kidney. (The tumor is here displaced downward from the position at the upper pole of the kidney which it maintained in life.)

partially constricted the great vessels in the region, including the vena cava, aorta, celiac axis and superior mesenteric artery. The neoplasm was not encapsulated. It was extremely lobulated, was pinkish gray and in general had a tense but not hard consistency. In some places it was soft and obviously necrotic. The general appearance was that of a rapidly growing, infiltrating carcinoma. Only a fragment of the right adrenal was recognizable, the remainder being fused with and destroyed by the tumor. The brain was normal on external inspection, but after fixation in formaldehyde, cut coronal sections showed a few small petechial hemorrhages in the parieto-occipital areas of the cortex. The pituitary gland was normal to external inspection.

Microscopic study showed the following significant changes: There was a streptococcic hemorrhagic pneumonia of short standing. There was a considerable

degree of fatty metamorphosis of the liver, particularly in the central zones, without other evidence of important passive congestion. There was no nephritis. The tumor was composed of sheets of cells without purposeful arrangements. The cells were epithelioid, were often as large as 15 to 20 microns in diameter and possessed slightly granular cytoplasms, and the nuclei were fairly rich in chromatin content. Variations in cell sizes and shapes were moderate. Mitotic figures were easily found, but were not numerous. The vascularity was low, and many areas of necrosis were encountered. A section of ovary showed occasional developing follicles in an otherwise normal and infantile gland. Sections of the pituitary gland showed a cyst, lined by cuboidal epithelium and filled with an eosinophilic, hyaline material, occupying the region of the pars intermedia and compressing the pars anterior. At the level of the greatest cystic enlargement the anterior lobe contained several small groups of basophilic cells, which, however, could hardly be termed adenomas.

CASE 5.—*Encapsulated carcinoma of the left adrenal gland in a 3 year old girl with hypertension (blood pressure 190 systolic and 160 diastolic); cardiac enlargement; cretinoid changes in the facies; lowered metabolic rate; cerebral atrophy and convulsions; death and autopsy.*

History.—B. J. B. was a girl 3 years 4 months old who was prematurely born at seven months, with a birth weight of 5 pounds (2,268 Gm.). Her development had been entirely normal until she was 3 years of age, at which time an increase in fat over the face and the extremities was first noticed. This fat gradually increased in amount and spread so as to involve the entire body during the ensuing four months. Nine weeks prior to hospital entry there was onset of right frontal headache, followed shortly by coma and convulsive movements of the eyes. This seizure lasted the greater part of a day, and from it the child spontaneously recovered. Similar attacks followed four weeks and six weeks later. During the last attack there were convulsive movements of the left arm, the left leg and the left side of the back, which lasted one hour. Recovery from the last attack was apparently complete except for some abnormality of gait, apparently due to mild spasticity.

Physical Examination.—The child was an obese white girl who appeared to be mentally retarded (fig. 14). Her height was 38 inches (96.5 cm.); her weight 33 pounds (15 Kg.). The face had a plethoric appearance (fig. 15). There was an indefinite bluish mottling of the skin over the arms. The generalized increase in subcutaneous fat was most marked over the face, chin and trunk. The fingers were tapered. The pupils reacted sluggishly to light. The fundi were negative. The heart on percussion proved to be enlarged. The genitalia were normal. The blood pressure was 190 mm. of mercury systolic and 160 mm. diastolic.

Laboratory Data.—Numerous examinations of the urine gave negative results. The specific gravity varied from 1.010 to 1.020. Two red cell counts were 4,940,000 and 5,910,000, respectively, with hemoglobin values of 100 and 110 per cent (Tallqvist). The spinal fluid showed a normal cell count and dynamics. The basal metabolic rate was —37. Results of sugar tolerance tests were: fasting level, 71 mg. per hundred cubic centimeters; after ingestion of 25 mg. of dextrose, one-half hour, 119 mg.; one hour, 116 mg.; one and one-half hours, 125 mg.; two hours, 116 mg., and three hours, 108 mg. The calcium content of the blood was 9.8 mg. per hundred cubic centimeters; the phosphrous content, 3.8 mg.; the serum globulin, 0.6 Gm.; the serum albumin, 6.0 Gm., and the nonprotein nitrogen, 33 mg. Roentgenograms showed the skull to be normal. A film of the chest showed marked cardiac enlargement, the transverse measurement of the heart being

10.4 cm. and the internal diameter of the chest being 17.2 cm. Films of the wrists showed a distinct retardation of osseous development when compared with the average normal.

Course.—Believing that the findings suggested the possibility of a tumor of the third ventricle, ventriculograms were made which showed markedly enlarged, asymmetric lateral ventricles, the right being somewhat larger than the left. There was also an excess amount of air over the surface of the cerebral cortex on both sides. The findings suggested a diffuse cerebral atrophy, more on the right, without evidence of neoplasm. An evaluation of the patient's mental status showed deterioration to the level of about 18 months. The blood pressure was repeatedly elicited between 180 systolic and 170 mm. diastolic and 190 systolic and 160 diastolic. During her hospital stay of eighteen days, there was one convulsive seizure lasting about ten minutes, during which the eyes were drawn to the left and there were clonic movements of the left leg and arm. Following this there was a period of drowsiness for eighteen hours.

After the patient's discharge from the hospital she was followed at home by her local physician for a period of one month until her death. During this time she was able to be up and around the house and was physically active. Suddenly she became very drowsy and had little interest in her environment. This deepened into coma and was associated with occasional spasms of the left leg and arm, the mouth and both eyelids. The blood pressure at this time was 260 systolic and 190 diastolic. She failed to rally, and died during the seizure, death occurring two days after the original onset of the stupor.

Pathologic Examination.—Autopsy was performed by the patient's home physician, and the following description is gleaned from his notes and from histologic study of sections of the pituitary gland and adrenal tumor which were submitted to us.

The brain was carefully searched for neoplasm, but none was found. There was some dilatation of the lateral ventricles. The pituitary gland was grossly normal. The heart was hypertrophied. In the left adrenal gland was a pinkish yellow tumor 3.5 by 2 by 1.8 cm.

Histologically, the pituitary gland showed nothing abnormal. There was no evidence of a basophilic adenoma or of hyperplasia of the basophilic cells.

Sections of the left adrenal gland showed an adenocarcinoma, which had apparently arisen in the substance of the gland and had expanded the gland. In one area the tumor was partially separated from the adjacent adrenal cortex by a thin capsule, but elsewhere these two structures appeared to merge. The tumor showed a fairly orderly arrangement of cells in cords and around alveolar spaces. The general architecture and type of cell often faintly resembled that of adrenal cortex. However, atypical forms of cells, disorderly arrangements and occasional areas with broad sheets of cells exhibiting rapid growth gave definite evidence of malignancy. There were a moderate number of mitotic figures, and we were forced to classify the neoplasm as a carcinoma of adrenal cortex origin.

CARCINOMA OF THE ADRENAL CORTEX IN THE MALE CAUSING GYNECOMASTIA AND LACTATION

While it is much more common for neoplasms of the adrenal cortex to produce signs of masculinization, there are at least 5 cases recorded in the literature in which the converse has been true, in which there have

been symptoms of femininization regarding hypertrophy of the breasts and even onset of lactation. Lisser reported 1 such case and collected 4 others. The ages of the male patients in these cases, however, were 44, 15, 26, 27 and 33 years, respectively. The patient of 15 years was the only one who might be regarded as being in the childhood group; hence the condition is one of extreme rarity in children.

NEOPLASM OF THE ADRENAL MEDULLA CAUSING HYPERTENSION (CHROMAFFINOMA OR PARAGANGLIOMA)

In the formation of the normal adrenal medulla, the immature cells (sympathogonia) develop into either ganglion cells or pheochrome cells, which constitute a large part of the fully formed medulla. From (1) the immature sympathogonia, (2) the ganglion cells or (3) the chromaffin cells there may arise, respectively, three types of medullary neoplasm. The first, and most common, is the neuroblastoma, or sympathicoblastoma, which is a highly malignant, rapidly growing and widely metastasizing growth which produces absolutely no endocrinologic disturbances and will not be considered here. The second type, relatively rare, is the benign ganglioneuroma, which likewise is inert from the hormonologic standpoint. The third type is the pheochromocytoma, or chromaffinoma—so called because of the affinity of its cytoplasmic granules for chromium salts—which produces an internal secretion and hence must be considered in this presentation. The last-mentioned lesion is an important surgical one, because the extreme hypertension which it causes can be completely relieved by removal of this slowly growing neoplasm.

The pheochromocytoma presumably brings about its distant effects by the discharge of large amounts of epinephrine into the blood stream. The important change, therefore, is to be found in the blood pressure, which exhibits elevations in the systolic levels above 200 or even 300 mm. of mercury, with a corresponding rise in the diastolic levels. It is rather characteristic for patients with such tumors to have hypertensive crises, which at first occur possibly every few weeks and later appear as often as three, four or more times a day. During such attacks, which may last from a few minutes to an hour or more, there is a generalized feeling of tenseness or tremulousness, followed by blanching of the skin, a feeling of pressure or discomfort in the epigastrium, nausea and finally palpitation or headache. Glycosuria has been described in some of these patients. Following the attack there are profuse sweating and exhaustion. The severity of the attacks increases to the point at which they are a danger to life, and, indeed, many of the patients die in the period of collapse which follows such a major hypertensive episode. Pulmonary edema is frequently listed as a cause of death.

As noted, the effects on the blood pressure are a constant finding, provided that examinations are made during the attack. In the patients whose blood pressure readings have been studied every ten or fifteen minutes before, during and after seizures, there has been a sharp rise of the systolic and diastolic levels during this period but a normal or only slightly elevated pressure between attacks. Such variations have been well illustrated by the studies of Coller, Field and Durant.

An occasional patient will notice that attacks are precipitated by pressing on the abdomen or else by bending the trunk to one side, such activities presumably compressing the tumor in such a way as to squeeze pressor substances from the tumor into the blood stream. Such pressure on the neoplasm may dramatically bring about attacks during physical examination and palpation of the upper part of the abdomen. Likewise, operative procedures which produce manipulation of the perirenal tissues—such as elevating the loin over a kidney bench—may lead to a catastrophe (Belt and Powell) even though the actual operative procedure is not begun.

Some of these tumors may be palpated through the abdominal wall, but the majority of them are small enough to elude detection by physical examination. If the growth is large, pyelography may show the kidney to be displaced downward or outward. However, it is not essential to demonstrate the neoplasm by physical examination or urologic investigation before proposing operation, because the observation of hypertensive crises and other effects of intermittent hyperadrenalemia is sufficient to warrant surgical exploration.

These hypertensive crises are presumably brought about by the discharge of epinephrine into the circulation, and confirmation of this is afforded by the observations of Beer, King and Prinzmetal, who demonstrated a pressor substance in the patient's plasma during attacks. Further proof of this is suggested by the analysis of tumor tissue for epinephrine in about a dozen cases and by the finding of contents as high as 3 to 4 Gm. of epinephrine per hundred grams of tumor in the case of Kalk and 2 Gm. per hundred grams of tumor in the case of Belt and Powell and also in the specimen described by Fein and Carman.

These tumors are about three times as common in females as in males. They may occur in elderly persons and are most common during the fourth, fifth and sixth decades, but such a tumor has been described in a patient as young as 2 years by Neusser and Wiesel. Kremer described a case with a paraganglioma of each adrenal gland in a girl 14 years of age. Chromaffinomas are somewhat more common in the right adrenal gland than in the left.

The tumors have varied in size from 1 to 15 cm. in greatest dimensions. Typical sizes vary from 2 or 3 up to 7 or 8 cm. in cross dimensions, but Belt and Powell described one weighing 1,000 Gm. The

smaller tumors are apt to be well preserved and have a grayish appearance, in contrast to the larger ones, which have a great tendency to hemorrhagic necrosis and cystic degeneration.

The tumors consist of nests or sheets of cells, which often have an arrangement in cords, giving an alveolar or trabecular appearance. Between such cords a fine supporting structure of connective tissue carries multiple capillary-sized vessels, giving the specimen a high degree of vascularity. The predominating cell is a large, polyhedral one, simulating the normal cells of the adrenal medulla but often being bigger than these. The nucleus is large, vesicular and rich in chromatin. A nucleolus is often seen. Mitoses are not common. The cytoplasm is granular, and by special staining methods these granules are found to take chromium salts, imparting to them a yellowish color—a characteristic which brands them as belonging to the chromaffin system. While more immature cells (pheochromoblasts) may not take the chromium stain, there are always a sufficient number of cells present which take the stain to make this examination of diagnostic importance. The chromaffin reaction is direct evidence of the presence of a strong reducing substance, which in all probability is epinephrine or an associated substance. The great majority of these tumors are benign, and metastases are rarely observed.

The technical details of operative removal of these neoplasms will not be considered here, but two precautionary measures should be stressed. First, the surgical approach should be transperitoneal, because this permits early ligation of the arterial supply and venous drainage before disturbing the tumor, whereas the lateral kidney approach necessitates considerable manipulation of the growth and discharge of epinephrine into the blood stream before the vascular pedicle can be reached. Second, the profound shock which usually follows removal of such a growth implies that the operator must be prepared to administer parenteral fluids or blood transfusions if necessary.

The complete relief of symptoms following successful removal of adrenal chromaffinomas makes it important to recognize the clinicopathologic process, for surgery has much to offer such patients.

PINEAL NEOPLASMS

Whether or not neoplasms of the pineal gland secrete a substance which is capable of bringing about the syndrome of "macrogenitosomia praecox" is highly debatable. However, the well known association of epiphysial tumor and precocious sexual development is sufficient to include a consideration of the condition in this presentation. Pubertas praecox may be found in association with (1) pineal tumors; (2) midbrain and hypothalamic tumors (Heuyer and his associates; Dods),

(3) inflammation of the midbrain (Thomas and Schaeffer), (4) adrenal cortical neoplasms and (5) testicular tumors (Rowlands, Nicholson and Parkes Weber).[3]

The classic picture of Pellizi's syndrome or pubertas praecox in conjunction with pineal neoplasm was well recorded by von Frankl-Hochwart and may be described as follows: The patients are always boys. Symptoms of varying degrees of intracranial pressure are produced by regional pressure on the aqueduct of Sylvius, thereby leading to internal hydrocephalus. Failing vision is common, and over 90 per cent of the patients have bilateral choking of the disk, usually of high degree. Involvement of the corpora quadrigemina by invasion or pressure is manifested in a high percentage of these patients by abnormalities in the oculomotor apparatus. Weakness of the internal or external rectus muscles is common, and about one third of the patients have a loss of conjugate movement of the eyeballs above the horizontal plane. Inequality of the pupils, with little reaction to light when good vision is retained, is occasionally found. Involvement of the inferior colliculi is manifested by some degree of central deafness in about half the cases. Pressure on the cerebral peduncles produces spasticity in the limbs in about half the cases, and the Babinski sign may be positive.

Endocrinologic disturbances are made evident by precocity in one or more of the sexual, somatic or mental spheres. The most striking changes are those of early development of the external genitalia with increase in the size of the testicles and penis, accompanied by growth of pubic hair. The unusual development of the genitalia may be well advanced in the second or third year of life. With such evidence of sexual maturation, the secondary sex characteristics are seen in a deepening of the voice and initiation of interest or advances toward members of the opposite sex. Somatic growth is not as striking as the sexual development and does not always accompany it, but it is not uncommon to find these boys increased in height, size and weight above the range of normal for the given age. About one quarter of the patients show some degree of adiposity. Mental precocity may be evident on casual observation, or some special aptitude may be discovered on more careful psychologic examination. Summarizing this clinical picture, it may be said that precocity in mental, bodily or sexual development, combined with signs of increased intracranial pressure and involvement of the corpora quadrigemina, is highly suggestive evidence of pineal neoplasm.

Pineal neoplasms producing endocrinologic disturbance are limited to childhood and preadolescence, but not all the tumors occurring in this lower age group give rise to precocity. In 1911 Pearce Bailey and

3. References to Heuyer and his associates, Dods and Thomas and Schaeffer are included in the bibliography on tumors of the floor of the third ventricle.

Jelliffe collected 60 cases of verified pineal growths in patients of all ages. In this group 20 patients were below the age of puberty, and only 7 showed marked evidence of premature adolescence. Horrax and Percival Bailey (1925) prepared a table of 14 cases—12 gleaned from the literature and 2 of their own—of pineal tumor in patients showing pubertas praecox. In 1936 Horrax published a report of an additional case of physical and sexual precocity in a boy of 10 years with strong ventriculographic evidence of pineal neoplasm but without pathologic verification of the lesion. There is no explanation for the onset of precocity in some persons and its absence in others with a neoplasm of similar size and histologic structure.

Pineal tumors have been found in both sexes, but the manifestations of endocrine disturbance have been limited to boys, with only one possible exception, a patient of Marburg's. This patient, a girl of 9 years, showed no disturbance of the sexual organs, and adiposity was the only metabolic change which might be regarded as abnormal.

The mechanism whereby pineal tumors give rise to sexual or somatic abnormalities is little understood. It is not known whether the endocrinologic changes are brought about by (1) secretion of a hormone by the tumor, (2) destruction of the pineal gland, with consequent removal of a sex-suppressing control, or (3) pressure activation of some nearby center, such as the pituitary gland or the hypothalamus. Regarding the first possibility, there is little evidence to date that the neoplasm secretes an activating substance which brings about changes of precocity. There is, however, some evidence that destruction of the epiphysis removes the normal control which is exercised by this gland during preadolescent years. In support of this theory, Horrax' experiments (1916*a*) suggested that pinealectomized guinea pigs had a hastened development of the sexual organs, manifested before maturity by a relative increase in size and weight of both the testes and the seminal vesicles. It is confusing, however, to observe some boys with apparent total destruction of the pineal gland by neoplasm who do not exhibit precocity. With reference to the third mechanism, whereby precocity is induced by disturbance of a center near the pineal gland, we have striking illustrations of precocity (in case 8) in which the picture of pubertas praecox was brought about by a hypothalamic or pituitary disorder. It is beyond the scope of this presentation to enter the controversial discussion which Krabbe has admirably considered. Suffice it to say that some pineal lesions do produce precocious development in the male child for reasons poorly understood.

The central location of these lesions within the skull makes it hazardous to expose and surgically extirpate them. However, the results published by Dandy, by Van Wagenen and by Harris and Cairns indicate that it is surgically possible to remove pineal neoplasms and restore

the individuals to a useful life. Moreover, Horrax (1936) has demonstrated that temporal decompression combined with roentgen irradiation may give striking temporary relief of symptoms.

I have not encountered a case of pineal neoplasm with pubertas praecox in our material and hence draw on the following example of a pineal lesion previously published by Horrax (1936) in the *Archives of Neurology and Psychiatry.*

CASE 6.—*Verified pineal neoplasm; typical findings of pubertas praecox in a 10 year old boy with symptoms of increased intracranial pressure; ventriculogram highly suggestive of pineal tumor; decompression and roentgen therapy.*

Fig. 17 (case 6).—A 10 year old boy with a pineal neoplasm, showing the marked physical overdevelopment, the adult size of the external genitalia and the internal strabismus of the right eye. The patient presented the typical picture of macrogenitosomia praecox (Horrax, 1936.)

History.—C. C. was a 10 year old boy in whom abnormalities had been noted for about one year. During this year he had gained 21 pounds (9.5 Kg.), and his height had increased considerably. He had also become extraordinarily well developed and muscular, his voice had changed to that of an adult, and the amount of facial and bodily hair had increased greatly. The external genitalia had likewise reached adult proportions. The patient had been in the third grade of school. For three weeks there had been a complaint of headache, and for ten days double vision had been noted.

Physical Examination.—The child presented the general development of a boy of 16 (fig. 17). The muscular development was extremely pronounced. There was abundant bodily hair, particularly on the lower parts of the legs and the

lower halves of the thighs. On the cheeks and the upper lip was a considerable growth of adolescent hair; axillary hair was present; pubic hair was adult in type and amount but feminine in distribution. The external genitalia were of adult appearance and proportions, the flaccid penis measuring 8.5 cm. in length and the testes being about the size of small pecan nuts. The testes were fully descended in the scrotum. The voice corresponded to the deep bass voice of an adult.

The pupils were equal and reacted fairly well to light and in accommodation, the right pupil being distinctly less active than the left. There was fairly well marked weakness of the right abducens nerve, making external rotation poor in the right eye. Otherwise the ocular movements were normal, including the conjugate movement upward. A few nystagmoid jerks were present on looking toward either side. The outlines of the optic disks were entirely obliterated, and the disks were elevated between 3 and 4 D. There were marked venous engorgement and tortuosity. Visual acuity was 20/50 on the right and 20/20 on the left. The fields were normal.

Fig. 18 (case 6).—Ventriculogram of a patient with a pineal neoplasm. Arrows point to the shadow of the tumor bulging into the posterior end of the dilated third ventricle (Horrax, 1936).

The child's weight was 97 pounds (43.5 Kg.), whereas one year before it had been 76 pounds (34.5 Kg.). The height was 57½ inches (145.9 cm.). The basal metabolic rate was 14. Before the patient had had any roentgen treatment, 10 cc. of his urine was injected into a capon. This produced in the capon a free growth of comb, spurs and tail plumes. The same amount of urine was injected into a capon after roentgen treatment, and no changes occurred. The blood pressure was 114 mm. of mercury systolic and 76 diastolic, which is possibly a little high for a boy of the patient's age. The preoperative diagnosis was probable pinealoma.

Operations.—A ventriculogram was carried out to confirm the preoperative diagnosis. The plates showed considerably dilated ventricles, with a large, distinct shadow bulging into the posterior portion of the dilated third ventricle (fig. 18).

The boy was treated by turning down a bone flap in the right occipital area, making a decompression in the anterior part of the field over the temporal region and subsequently instituting roentgen treatment. This therapy afforded considerable

amelioration of symptoms. A personal communication from Dr. Horrax states that one year later the diagnosis was verified by the removal of a large pinealoma.

TUMORS OF THE FLOOR OF THE THIRD VENTRICLE.

Little has been written about cases of striking physical and sexual maturation in children of either sex with neoplasms involving the infundibulum or floor of the third ventricle. Our attention was first focused on this lesion in case 7, in which we blundered through operative exploration of the abdomen for the possibility of ovarian neoplasm and then exploration of the pineal area for possible pineal tumor, only to find at autopsy a hamartoma at the base of the brain which extended into the floor of the third ventricle. On reviewing our material it becomes apparent that we have encountered this symptom complex in several other patients, and on reference to the literature I find that the condition has been admirably described by Le Marquand and Russell in a male patient.

The manifestations of this lesion of the central nervous system are usually seen early in life, the 2 cases here presented being rather typical in that in the first the patient was 1 year of age and in the other, 3 years of age, when symptoms were first noted. The outstanding findings are (1) precocious maturation of the genitalia, adhering to the sex of the child, (2) appearance of secondary sex characteristics, (3) excessive somatic development, (4) advancement in the bone age as determined by epiphysial development and fusion, (5) possibly a disturbance in the water balance and (6) minimal or no signs of an expanding intracranial lesion. These six considerations may be treated more fully as follows:

Increase in size and development toward the adult type of genitalia is found in either the male or the female. In the male, the prostate and the seminal vesicles are enlarged. The 7 year old boy in case 8 possessed testicles and penis almost the size of a man's, and pubic hair was long and abundant. Erections were frequent, and ejaculations questionably occurred. Subsequent pathologic examination of the testicles showed germinal epithelium well advanced to production of spermatids and spermatozoa. While there had been no abnormal advances toward members of the opposite sex, the boy of 3 years of age reported on by Le Marquand and Russell became a nuisance because of overt sexual acts toward women. In the female there is also a striking genital development, as judged by the size and configuration of the external organs and by hypertrophy of the labia and the mons veneris, with a sparse growth of pubic hair. In conjunction with these changes of the external genitalia, there is evidence of activated function of the internal organs as shown by the onset of menstrual flow.

The development of secondary sex characteristics is an outstanding feature. In the male the bodily contour changes to simulate the adult form, with widening and squaring of the hips and shoulders as well as

an increase in skeletal muscle and strength. The voice becomes husky and deep, and in the patient in case 8 it was astounding to "hear a deep bass voice emerge from a child of seven years." In the female the enormous development of the breasts exceeds that seen in any other form of endocrinologic disturbance in childhood. The breasts are firm and well rounded, and histologically hyperplasia of the ducts and acini of the glands of Montgomery completes the picture of local response to stimulation by internal secretory products.

Excessive somatic growth is evident in both sexes. In case 8 a boy of 7 years was as large as a youth of 12 or 13 years, and in case 7 the girl of 2 years was fully as tall as a child of 4 years. This increased

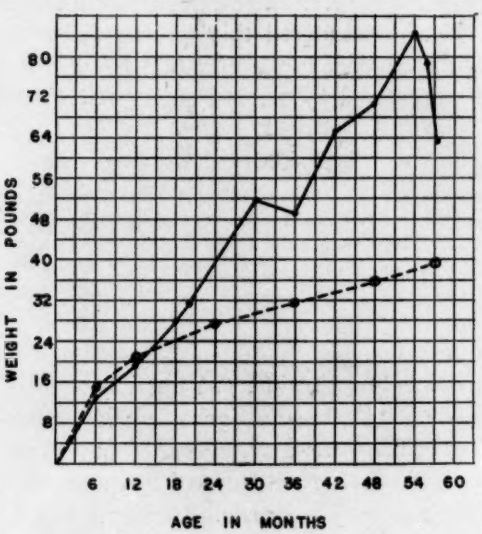

Fig. 19.—Weight chart of Le Marquand and Russell's patient with a tumor in the floor of the third ventricle associated with marked physical and sexual precocity. The solid line indicates the weight of the patient, the dotted line, that of a normal boy (chart modified from Le Marquand and Russell).

growth is not limited to height alone, for there is enhancement in size of the soft tissues, and these children tend to be thickset and greatly above the expected weight for their age. This great increase in weight is well portrayed by the graph (fig. 19) which shows the course of Le Marquand's patient. Some degree of obesity is common, and the extent of this is seen in figures 20 and 21, which show the heavy rolls of fat about the trunk. Great strength, in the male at least, is seen in some cases. This is well illustrated by Le Marquand's patient, who could accurately steer a farm tractor at 3 years of age.

Advancement in osseous growth is a feature of all cases. This is best observed by roentgenologic examinations of the carpal bones (fig. 22).

Fig. 20 (case 7).—A 2 year old girl with a hamartoma in the hypothalamus and the floor of the third ventricle. Note the advanced physical development, the rolls of fat around the abdomen and the precocious development of the breasts.

Fig. 21 (case 8).—A 7 year old boy with excessive physical and sexual development associated with a ganglioneuroma at the base of brain. Note the muscular appearance, the hairiness of the legs, the pubic hair and the adult size of the external genitalia.

but additional evidence of early epiphysial calcification and fusion is seen in the long bones and in the bones of the pelvis. Le Marquand and Russell tabulated the advanced growth exhibited by their patient, who was studied from the ages of 32 to 58 months, as follows:

Patient's age at examination....	32 months	46 months	58 months
Hand	7-11 years	13-15 years	13-15 years
Foot	5-14 years		15-20 years
Elbow	8-13 years	12-14 years	14-17 years
Pelvis	10-15 years	13-16 years	15-17 years
Average (Approx.).....	10 years	14 years	16 years

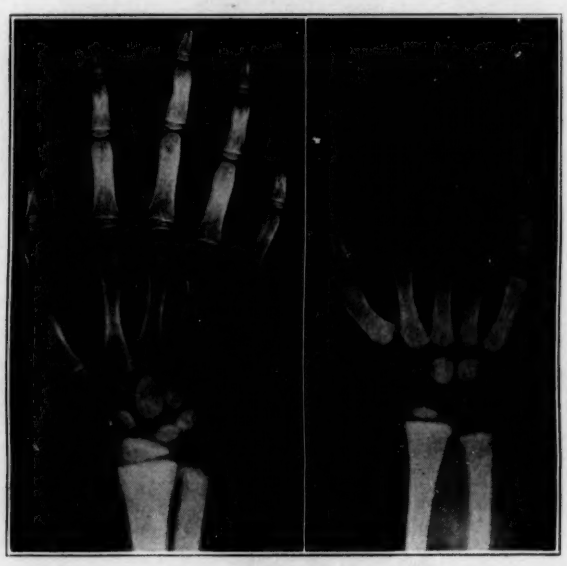

Fig. 22 (case 7).—Roentgenogram of the wrist of the same patient as in figure 20 (left), showing the advanced bone development when compared with that of a normal girl of the same age (right).

Similar advancement in the bone age is seen in our cases 7 and 8, in which a girl of 2 years had carpal bones consistent with an age of 5 years and a boy of 7 years possessed bony development consistent with that of a person of 18 years.

The dentition may show some advancement. We do not have any observations in this regard from our material, but Le Marquand and Russell published data which was studied from roentgenograms. Up to the age of 3 years, 11 months the development appeared to be approximately normal, but there was a notable advance in the ensuing year. "Judging from the absorption of the roots of the upper temporary incisors, the shedding of the lower temporary central incisors, and the

state of calcification of the permanent dentition, the child appears to be about fifteen months in advance of normal."

An increase in arterial blood pressure is not a prominent finding, and indeed, is not a constant finding. In Le Marquand and Russell's case it was 90 mm. systolic and 60 diastolic, but in our 2 year old child it was 112 systolic and 66 diastolic, and in the 7 year old boy it was 130 systolic and 90 diastolic.

Disturbances in water balance were noted in both our patients. In the girl this was not discovered until attempts were made to collect specimens of twenty-four hour urine for assay of excreted hormones. The output was so low, in contrast to a normal fluid intake, that it was thought we were losing portions of the specimens. However, repeated observations on a metabolism frame disclosed that the average daily output of urine was 90 to 150 cc., and at no time did it exceed 200 cc. The concentration of the urine was normal. While oliguria was found in this case, in the other case there was a distinct polyuria, which was noticed by the patient long before hospitalization. It appears, then, that neither oliguria or polyuria is characteristic, but that disturbance in either the fluid intake or the output is likely to accompany these lesions which, by pressure or invasion, involve the tuber cinereum or the third ventricular floor.

Signs of an expanding intracranial lesion may be entirely wanting or may be obvious, but it is rather characteristic for them to be minimal. During observations over two years, Le Marquand and Russell found no clinical evidence of a lesion of the central nervous system. In our younger patient many observers failed to discover any neurologic abnormality, but a subsequent reexamination revealed extremely slight weakness on one side of the body, suggesting involvement of the cerebral peduncles. In the older child visual disturbances, related to weakness in the extraocular motor apparatus, were the chief complaint on entry to the hospital. On physical examination choking of the optic fundi, paresis of the external rectus muscle of one eye and hydrocephalus all pointed with certainty to an intracranial growth.

The lesions which cause this astounding syndrome lie in the interpeduncular fossa at the base of the brain. They may be attached to the tuber cinereum or the mamillary bodies and may invade the hypothalamus. It appears to be common for them to arise from or to be attached to the floor of the third ventricle. This mass of abnormal tissue filling the space between and anterior to the cerebral peduncles was as small as 1.35 by 0.8 by 1.5 cm. in Russell's specimen and as large as 4.5 by 3 by 4 cm. in our case 7 (fig. 23). The histologic structure in each instance has been that of a slowly growing tissue of neurologic origin. The example studied by Heuyer, Lhermitte, de Martel and Vogt was described as an ependymoglioma. In our case 8 the findings were

characteristic of ganglioneuroma. Le Marquand and Russell described a histologic picture similar to that in case 7, namely, a purposeless admixture of neurons and various types of supportive glial cells, without

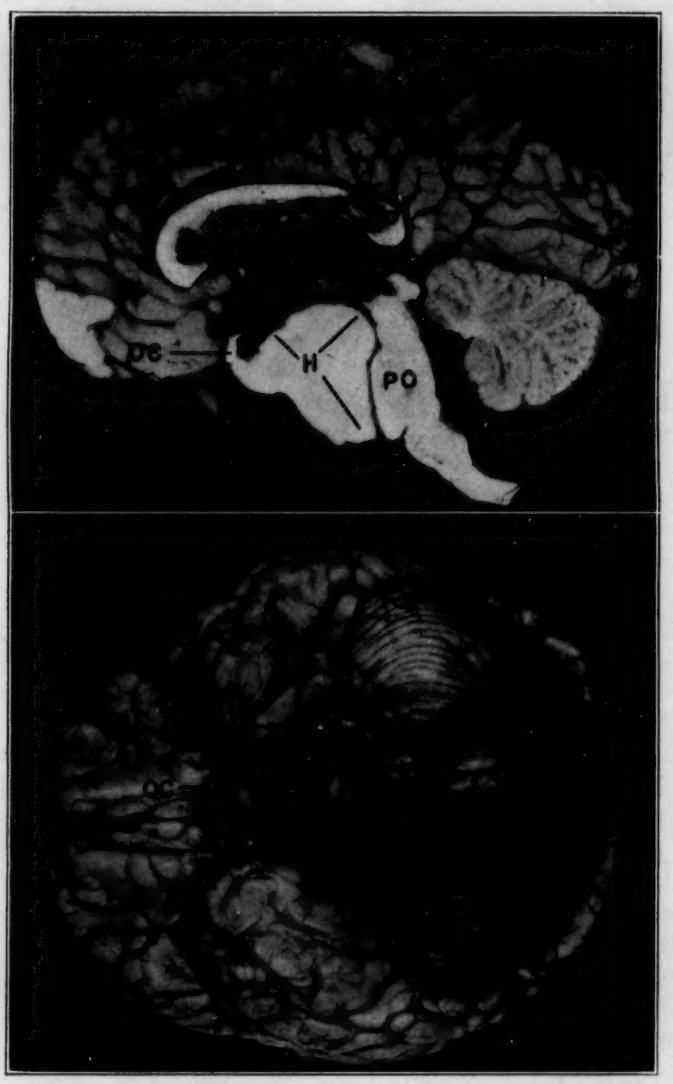

Fig. 23 (case 7).—Brain of a 2 year old girl with sexual and somatic precocity, showing a large hamartoma at its base. *H*, hamartoma; *OC*, optic chiasm; *PO*, pons.

evidence of invasive growth, but blending gradually with nearby normal brain structures—findings which are poorly classed as neoplasm and are better listed as hamartoma.

The mechanism whereby these "tumors" of the third ventricle bring about such profound endocrinologic disturbances is little understood. The partial involvement of the hypothalamus in our case 7 would suggest that some local stimulation might produce these distant effects, but the direct evidence in other cases that the hypothalamus is normal, both by gross and by microscopic examination, makes this explanation unlikely. Internal hydrocephalus (Dorff and Shapiro) is known to bring about physical and sexual changes similar to the ones here described, but the complete absence of hydrocephalus in some of the cases leaves little to support this hypothesis. The involvement of the floor of the third ventricle in all cases by pocketing, attachment or partial replacement of this structure makes plausible the theory that disturbance of these centers may alter the pathways which are known to extend to the pituitary body and thereby bring about endocrinologic disturbances indirectly by way of this gland. Finally, it is conceivable that a mass of tissue, whatever its nature, situated beneath the third ventricle, pressing on the tuber cinereum and pituitary stalk, might by its mere presence partially compress and obstruct neighboring veins and thereby cause hyperemia of the pituitary body. Such a state of vascular congestion, which obviously must exist to some degree, could conceivably stimulate the hypophysis to increased activity and thereby induce the clinical picture described. While all of these hypothetic explanations are of interest, they are of less importance than the establishment of the fact that lesions of the interpeduncular fossa can produce the picture of macrogenitosomia praecox in both male and female children.

CASE 7.—*Astrocytic hamartoma in the hypothalamus and in the floor of the third ventricle; 2 year old girl with beginning menstruation, great development of the breasts, hypertension, increased bone growth and oliguria; death; autopsy disclosing a large astrocytic lesion at the base of the brain.*

History.—B. S. was a 26 month old girl who had been apparently normal in development until 19 months of age, when a sudden increase in the size of the breasts was first noted and there was a discharge of about ½ ounce (15 cc.) of unclotted blood from the vagina during a twenty-four hour period. At the same time some hairs on the vulva first appeared. At 24 months of age the areolas of the breasts became quite pigmented, and pubic hair was noted. During the last month prior to hospitalization there was a striking increase in bodily dimensions and in the deposition of bodily fat. Since the age of 1 year there had been a gradual increase in the pigmentation of the skin. Her speech had been somewhat retarded, and though she spoke but few words, her intelligence seemed normal.

Physical Examination.—The patient was a mentally alert, obese child with the outstanding characteristic of precocious enlargement of the breasts (figs. 20 and 24). There was a widespread and heavy accumulation of subcutaneous fat, which was particularly prominent in rolls around the waist and the abdominal wall. The skin of the face, body and extremities was diffusely and evenly pigmented more than normal, giving her a slightly negroid appearance. The areolas of the breasts were heavily pigmented. The skin was thicker and firmer than normal for a

child of this age. The lips were full and thick. A few fine short hairs were present over the vulva. The optic fundi were negative except for a slight blurring of the nasal margins of the disks. By rectal examination the uterus was felt to be definitely enlarged. The height was 38½ inches (97.8 cm.); the weight, 37¼ pounds (16,896 Gm.); the pulse rate, 110; the blood pressure, 112 mm. of mercury systolic and 66 mm. of mercury diastolic.

Laboratory Data.—Three blood counts showed from 5,100,000 to 5,600,000 red cells per cubic millimeter, 9,500 to 16,000 white cells and 85 to 100 per cent hemoglobin, with essentially normal differential cell counts. Frequent examinations of urine gave negative results. There was good concentration, as high as 1.025. Chemical studies of the blood showed the following composition: cholesterol 127 mg. per hundred cubic centimeters, calcium 9 mg., phosphorus 4 mg., phosphatase 12 Bodansky units, nonprotein nitrogen 26.5 mg. and serum

Fig. 24 (case 7).—Same patient as in figure 20, showing better the enlarged breasts, the heavy pigmentation of the areolas, the obesity, the fulness of the lips and the negroid appearance.

protein 7.1 Gm.; chlorides 106 mg. per liter and sodium 138 mg. The results of a dextrose tolerance test were: fasting level, 91 mg. per hundred cubic centimeters; and fifteen minutes after ingestion of dextrose, 191 mg.; forty minutes after, 250 mg.; seventy-five minutes after, 129 mg.; one hundred and thirty-five minutes after, 100 mg. Smears of the vaginal secretions showed cornified epithelial cells. Roentgenograms of the skull showed no pathologic conditions. Films of the extremities showed an increased calcification and development of the carpal bones and epiphyses corresponding to an age of about 5½ years (fig. 22). Studies of the excretion of estrogen in twenty-four hour specimens of urine showed the following number of mouse units on separate days: 405, 324, 648, 36, 175, 270 and 12. Studies for excretion of gonadotropic substance in the urine gave negative results, except for one specimen which showed a questionably positive reaction.

Course.—Frequent determination of the blood pressure showed it to vary from 130 to 100 mm. of mercury systolic and from 9 to 60 mm. of mercury diastolic, the usual pressure being around 110 systolic and 80 diastolic. Twelve days after admission to the hospital, vaginal bleeding again started and continued for three days, the amount being copious for the first twenty-four hours. Lumbar puncture disclosed normal fluid and dynamics. Studies of the water balance showed an intake varying from 270 to 1,120 cc., with an average of around 500 cc. The urinary output varied from 150 cc. to 200 cc., and in one twenty-four hour period it was as low as 90 cc. The differential diagnosis lay between an ovarian neoplasm of the granulosal cell type and a neoplasm invading the pituitary gland or hypothalamus. While most of the symptoms could best be explained on the basis of an intracranial lesion, it was decided to explore the abdomen and pelvis.

At pelvic exploration, the uterus was found enlarged to the size of that which would be normal for an 8 or 10 year old girl. The ovaries were about 3 cm. in length and 2 cm. in diameter. The right one was removed for study, and the left one was transected, but no neoplasm was found in its interior. The split left ovary was then sutured together and left in place. No neoplasm could be felt in the adrenal region or in any other part of the abdominal cavity.

After the patient's recuperation from the laparotomy, encephalograms were made which showed enlarged lateral, third and fourth ventricles. Three small nodular masses could be seen projecting into the posterior portion of the third ventricle. Believing that these findings and the patient's symptoms were consistent with a pineal neoplasm, we performed a cranial exploration through a large left occipital osteoplastic bone flap. An adequate exposure of the pineal region showed no abnormality. Recovery from the cranial exploration was uneventful until the fifth day, when there was onset of drowsiness, generalized convulsions and fever, which were followed in a few hours by death.

Pathologic Examination.—Complete autopsy showed the same external changes noted during life. Only the observations which appear to pertain to the present discussion will be listed here. The thyroid weighed 4 Gm. The thymus weighed 29 Gm. The heart weighed 100 Gm. (expected normal weight, 56 Gm.). The liver weighed 730 Gm. (expected normal weight, 394 Gm.). The adrenal glands weighed 3.5 and 4 Gm., respectively. The uterus measured 4.5 cm. from the external os to the top of the fundic cavity. The endometrium was 2 mm. thick, and the myometrium had a maximum thickness of 0.9 cm. The remaining left ovary measured 3.5 by 2.2 by 1.6 cm. The pituitary gland was grossly normal. At the base of the brain there was a yellowish white mass which extended from the optic chiasm to the pons (fig. 23). This measured 4.5 cm. in length and varied from 3 to 4 cm. in width. It was well encapsulated—as viewed from the base of the brain—and had a uniformly firm and elastic consistency. After fixation in solution of formaldehyde, a midsagittal section of the brain was made. This gave an excellent view of the abnormal mass, a mass which arose from the floor of the third ventricle and the mamillary bodies, partially involved the hypothalamus on either side and projected slightly into this cavity, but principally bulged down below the inferior surface of the brain. It compressed the optic chiasm and the tuber cinereum forward and the pons backward, but was demarcated from all these structures by the leptomeninges. The ventricular system was dilated.

Microscopically, there were the following important observations: Glycogen deposits in the liver were increased. The ovary showed mature graafian follicles. A large part of the ovary was replaced by follicular cysts. The endometrial glands were much larger than those normally seen at this age. The vaginal mucous

membrane had a greatly increased number of squamous cells but no true keratinization. There was hyperplasia of the alveoli of the breast. In the pituitary gland there was no adenoma or hyperplasia of the basophilic cells. The acidophilic cells appeared to be somewhat more numerous than normal. Sections from the basilar mass showed an unusual tissue of the neurologic series. It was composed principally of a fine, fibrillary, glial meshwork with a rather low cellularity. Most of the presenting cells were of the microglia type, but a few fibrillary astrocytes and occasional protoplasmic astrocytes were also encountered. There were no ganglion cells. No mitotic figures were seen. The tissue was well preserved, and while no necroses were present, there were scattered small calcific concretions. This abnormal tissue merged imperceptibly with the floor of the third ventricle. The absence of evidence of active growth and invasive qualities made it necessary to classify the lesion as a hamartoma.

The following case is that of a patient who was originally studied at the Children's Hospital and was later transferred to the Peter Bent Brigham Hospital, where he was operated on by Dr. Harvey Cushing. A report was made by Horrax and Bailey in the *Archives of Neurology and Psychiatry.*

CASE 8.—***New growth at the base of the brain in a 7 year old boy with evidence of sexual precocity, polydipsia, polyuria and advanced bone growth; ganglioneuroma in the floor of the third ventricle; attempted removal of a portion of the neoplasm; death.***

History.—R. R. was a 7 year old boy who entered the hospital primarily because of visual disturbances. One year previously it had been first noted that there was an internal squint of the right eye. For the preceding two weeks there had been double vision. The patient had "always" had a large appetite and had "always" drunk large amounts of water. For one month there had been frequent urination, as often as every half-hour during the day and every two or three hours during the night. Axillary and pubic hair had first appeared at the age of 3 years and soon afterward reached full adult development. During these changes in the third year there were also a marked development in the external genitalia and a concomitant deepening of the voice. There had been gradual development of adiposity since the third year.

Physical Examination.—The boy was strikingly mature in his physical development, which was fully that of an adolescent youth (fig. 21). The head was large. When the skull was tapped, a cracked pot resonance confirmed the impression of hydrocephalus. The trunk and limbs were stout and were thickly covered with coarse hair. His long body and short extremities suggested achondroplasia. The hands and feet were short, squat, thick and pudgy. There was considerable bowing of the legs. The height and weight were 56 inches (142 cm.) and 110 pounds (50 Kg.), as compared with 44 inches (112 cm.) and 50 pounds (23 Kg.), the expected normal figures for his age. There was a slight internal strabismus of the right eye. The external genitalia were fully developed and were the size of those of an adult. Pubic hair was well developed. The blood pressure was 130 mm. of mercury systolic and 90 mm. diastolic. The voice was extremely mature, and it was astounding to hear such a deep bass voice emerge from the lips of this child of 7 years. There was increased perspiration over the whole surface of the body. There was marked generalized adiposity. There was bilateral choking of the optic disks to 3 diopters.

Laboratory Data.—Specimens of urine showed concentrations of 1.008 to 1.017. Three of nine specimens contained from the slightest possible trace to a slight trace of albumin. Twenty-four hour amounts of urine varied from 1,450 to 1,900 cc. The blood count on admission was 4,760,000 red cells per cubic millimeter and 14,200 white cells. A sugar tolerance test showed no urinary dextrose after oral ingestion of 50 Gm. of dextrose. The basal metabolic rate was —24. Roentgenograms of the skull showed a thin vault without localized changes. The pituitary fossa was normal in size, shape and position, and just above it there was an irregular, dense mass of calcification, shaped like a mushroom, with the stalk pointing toward the pituitary fossa. Posteroanterior films showed a calcified mass in the midline but extending somewhat more to the right than to the left. The impression was gained at the time that these changes represented a suprasellar cyst. A film of the right hand and wrist showed all of the epiphyses fused except those of the radius and ulna, and the latter was partially fused. These findings were compatible with the development of an 18 year old person.

Course.—While the clinical findings of pubertas praecox and choking of the optic disks strongly suggested the presence of a pineal neoplasm, there were no symptoms suggesting involvement of the corpora quadrigemina or the cerebellar peduncles, which should have accompanied an expanding pineal lesion. Believing that the patient had a suprasellar cyst, and in the hope of relieving his badly choked optic disks, Dr. Harvey Cushing undertook operation. Exploration was made through a right transfrontal osteoplastic bone flap. The optic chiasm was found to be normal. The corpus callosum was exposed, and on puncture of it there was a great gush of clear fluid. On incision of the corpus callosum, a rounded, firm and partially calcareous mass was disclosed lying between the two lateral ventricles and blocking the foramens of Monro. Believing that the corpus callosal incision would allow fluid to escape from the ventricles to the subarachnoid spaces and thereby relieve the intracranial pressure, he made no attempt to remove the tumor.

During the following eight days the patient made a good recovery from the operation, but it was evident that the intracranial pressure was not relieved. A second exploration was therefore undertaken for direct attack on the tumor. The frontal flap was reelevated, and the tumor was viewed through the old corpus callosum incision. Bits of the tumor were cut away so that the foramens of Monro could be visualized and left unobstructed. During the latter part of the operation the respirations were shallow, and there were long periods of apnea. The wound was closed, but the patient never completely recovered consciousness. The pulse increased slowly; hyperthermia (to 108 F.) developed during the first postoperative night, and death ensued twenty hours after operation.

Pathologic Examination.—Autopsy showed the general bodily features noted during life. Thymic tissue was present, and when dissected free it was found to weigh 12.5 Gm. The heart weighed 200 Gm. (expected normal weight for age, 100 Gm.). The kidneys weighed 130 and 140 Gm., respectively. The thyroid, the parathyroids and the adrenal glands were normal in appearance and size. The testicles were enlarged (fig. 25) and measured 4.5 cm. in length and nearly 3 cm. in diameter. The prostate was considerably enlarged for a boy of this age, and was more nearly the size normal for a boy at puberty. Smears of secretion taken from the opened prostate showed many well developed spermatozoa, which, however, were not active (autopsy performed four and one-half hours after death).

The frontal portion of the brain showed evidence of the recent operative procedure. After fixation in solution of formaldehyde, the brain was sectioned longitudinally in the midline (fig. 26). The anterior part of the corpus callosum had

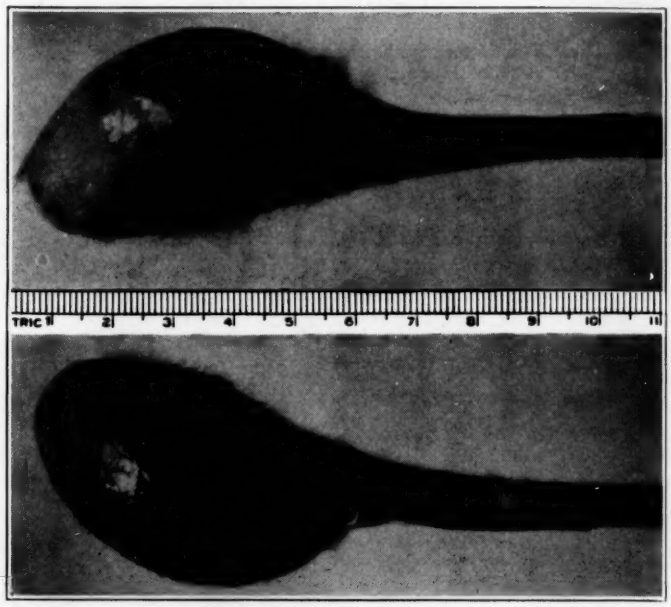

Fig. 25 (case 8).—Adult-sized testicles from a 7 year old boy with third ventricular lesion and macrogenitosomia praecox.

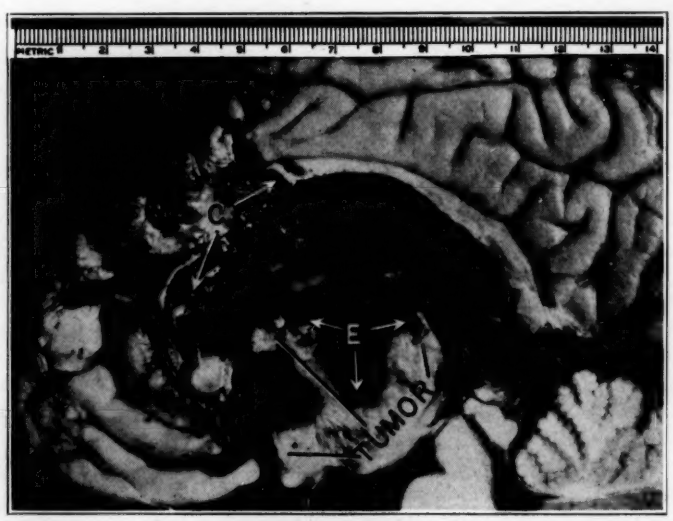

Fig. 26 (case 8).—Ganglioneuroma in the floor of the third ventricle which produced hydrocephalus by blockage of the foramens of Monro in a patient with marked sexual and physical precocity (Horrax and Bailey). *C*, corpus callosum defect, following operation; *E*, excavated portion which was exposed and removed at operation.

been previously divided to permit access to the tumor. The growth was a large, rounded mass about 5 cm. in diameter, which largely replaced the floor of the third ventricle and projected upward into this ventricle and completely blocked the foramens of Monro. Only the superior portion of the tumor had been gutted in the previous attempts at extirpation. The tumor extended downward to the very stalk of the hypophysis. The pituitary gland was grossly normal. The pineal body was of normal size.

Histologically, the testes showed active spermatogenesis, and numerous spermatozoa were found in each epididymis. The prostate was glandular and was of a fully developed adult type. The adrenal glands showed no recognizable abnormalities. Sections of the pituitary gland showed several small cysts but no other apparent abnormality. Tissue from the third ventricle mass showed a neoplasm composed of cells of the neurologic series. The nuclei varied considerably in size and appearance. Many of the cells possessed cytoplasms which were small and well defined, but others were without visible cytoplasmic borders. Some cells had large, pale-staining oval nuclei and abundant cytoplasm, imparting the appearance of ganglion cells. Large numbers of rather short, coarse, neuroglial fibrils appeared between the cell nuclei. Multiple small calcific concretions were scattered through the tumor tissue. The growth could best be classified as a ganglioneuroma.

SUMMARY

For the benefit of students and clinicians who encounter and must diagnose endocrine disturbances of childhood, a group of cases is presented to point out the sexual, somatic and functional aberrations which are produced by tumors arising in the glands of internal secretion. Neoplastic diseases of the ovary, testicle, adrenal medulla, adrenal cortex, pineal body and hypothalamic centers are individually considered, and the clinical picture of each condition is presented. An attempt is made to stress the clinical findings which will aid in determining which organ is the focus of the primary disease. The endocrine disturbances resulting from the various types of neoplasms are illustrated by reports of representative cases.

Dr. Sidney Farber, pathologist at the Children's Hospital, gave permission to use pathologic material which he has collected, studied and preserved. Dr. William E. Ladd gave permission for the use of cases from his surgical service at the Children's Hospital.

BIBLIOGRAPHY

GENERAL

Nathanson, I. T.; Towne, S. E., and Aub, J. C.: The Daily Excretion of Urinary Androgens in Normal Children, Endocrinology **24**:335, 1939.

——Farber, S.; Cutler, C. H., and Aub, J. C.: The Generalized Effects of Hyperfunctioning Endocrine Tumors in Childhood, read before the Third International Cancer Congress, Atlantic City, N. J., Sept. 11-15, 1939; to be published.

Reilley, W. A.; Lisser, H., and Hinman, F.: Pseudo-Sexual Precocity: The Adrenal Cortical Syndrome in Preadolescent Girls, Endocrinology **24**:91, 1939.

Rowlands, R. P.; Nicholson, G. W., and Weber, F. P.: Growth of the Left Testicle with Precocious Sexual and Bodily Development (Macro-Genito-Somia), Guy's Hosp. Rep. **79**:401, 1929.

Talbot, N. B.: The Effect of Estrogen on the Skeletal Age of Immature Rats, Endocrinology **25**:325, 1939.

Todd, T. W.: The Atlas of Skeletal Maturation, St. Louis, C. V. Mosby Company, 1937.

Vogt, E. C., and Vickers, V. S.: Osseous Growth and Development, Radiology **31**:441, 1938.

NEOPLASMS OF THE OVARY

Bland, P. B., and Goldstein, L.: Granulosa Cell and Brenner Tumors of the Ovary, Surg., Gynec. & Obst. **61**:250, 1935.

Meyer, R.: The Pathology of Some Special Ovarian Tumors and Their Relation to Sex Characteristics, Am. J. Obst. & Gynec. **22**:697, 1931.

Novak, E.: Masculinizing Tumors of the Ovary (Arrhenoblastoma, Adrenal Ovarian Tumors), Am. J. Obst. & Gynec. **36**:840, 1938.

——and Gray, L. A.: Clinical and Pathological Differentiation of Certain Special Ovarian Tumors: Granulosa Cell Carcinoma, Arrhenoblastoma, Disgerminoma, Brenner Tumor, ibid. **31**:213, 1936.

Taylor, H. C.: The Pathology of the Ovarian Hormone, with Special Reference to Its Role in Tumor Development, Am. J. Obst. & Gynec. **36**:332, 1938.

Taylor, J. M.; Wolfermann, S. J., and Krock, F.: Arrhenoblastoma of the Ovary, Surg., Gynec. & Obst. **56**:1040, 1933.

NEOPLASMS OF THE ADRENAL CORTEX

Cahill, G. F.: The Adrenogenital Syndrome and Adrenocortical Tumors, New England J. Med. **218**:803, 1938.

——Loeb, R. F.; Kurzrok, R.; Stout, A. P., and Smith, F. M.: Adrenal Cortical Tumors, Surg., Gynec. & Obst. **62**:287, 1936.

Close, H. G.: The Incidence of Adenoma of the Pituitary Body in Some Types of New Growth, Lancet **1**:732, 1934.

Collett, A.: Genito-Suprarenal Syndrome (Suprarenal Virilism) in a Girl One and a Half Years Old, with Successful Operation, Am. J. Dis. Child. **27**:204 (March) 1924.

Frank, R. T.: A Suggested Test for Cortical Adrenal Carcinoma, J. A. M. A. **109**:1121 (Oct. 2) 1937.

Graef, I.; Bunim, J. J., and Rottino, A.: Hirsutism, Hypertension and Obesity Associated with Carcinoma of the Adrenal Cortex, Arch. Int. Med. **57**:1085 (June) 1936.

Lisser, H.: A Case of Adrenal Cortical Tumor in an Adult Male Causing Gynecomastia and Lactation, Endocrinology **20**:567, 1936.

McQuarrie, I.; Johnson, R. M., and Ziegler, M. R.: Plasma Electrolyte Disturbance in Patient with Hypercorticoadrenal Syndrome Contrasted with That Found in Addison's Disease, Endocrinology **21**:762, 1937.

Walters, W., and Kepler, E. J.: Adrenal Cortical Tumors and Their Treatment: A Study of Seven Operated Cases, Ann. Surg. **107**:881, 1938.

——Wilder, R. M., and Kepler, E. J.: The Suprarenal Cortical Syndrome with Presentation of Ten Cases, ibid. **100**:670, 1934.

NEOPLASMS OF THE ADRENAL MEDULLA

Beer, E.; King, F. H., and Prinzmetal, M.: Pheochromocytoma with Demonstration of Pressor (Adrenalin) Substance in the Blood Preoperatively During Hypertensive Crises, Ann. Surg. **106**:85, 1937.

Belt, A. E., and Powell, T. O.: Clinical Manifestations of the Chromaffin Cell Tumors Arising from the Suprarenal Medulla: Suprarenal Sympathetic Syndrome, Surg., Gynec. & Obst. **59**:9, 1934.

Brunschwig, A.; Humphreys, E., and Roome, N.: The Relief of Paroxysmal Hypertension by Excision of Pheochromocytoma, Surgery **4**:361, 1938.

Coller, F. A.; Field, H., Jr., and Durant, T. M.: Chromaffin Cell Tumor Causing Paroxysmal Hypertension, Relieved by Operation, Arch. Surg. **28**:1136 (June) 1934.

Edward, D. G.: Pheochromocytomata and Hypertension, with Details of a Case, J. Path. & Bact. **45**:391, 1937.

Eisenberg, A. A., and Wallerstein, H.: Pheochromocytoma of the Suprarenal Medulla (Paraganglioma), Arch. Path. **14**:818 (Dec.) 1932.

Fein, M. J., and Carman, F. F.: Medullary Carcinoma of the Suprarenal Gland (Pheochromocytoma), Am. J. Cancer **29**:301, 1937.

Howard, J. E., and Barker, W. H.: Paroxysmal Hypertension and Other Clinical Manifestations Associated with Benign Chromaffin Cell Tumors (Pheochromocytomata), Bull. Johns Hopkins Hosp. **61**:371, 1937.

Kalk, H.: Paroxysmale Hypertension: Blutdruckkrisen und Tumor des Nebennierenmarkes, Klin. Wchnschr. **13**:613, 1934.

Kremer, D. N.: Medullary Tumor of the Adrenal Glands, with Hypertension and Juvenile Arteriosclerosis, Arch. Int. Med. **57**:999 (May) 1936.

Neusser, E., and Wiesel, J.: Die Erkrankungen der Nebennieren, ed. 2, Vienna, Alfred Hölder, 1910, p. 97.

Palmer, R. S., and Castleman, B.: Paraganglioma (Chromaffinoma, Pheochromocytoma) of the Adrenal Gland Simulating Malignant Hypertension: Report of a Case, New England J. Med. **219**:793, 1938.

Rabin, C. B.: Chromaffin Cell Tumor of the Suprarenal Medulla (Pheochromocytoma), Arch. Path. **7**:228 (Feb.) 1929.

Wells, A. H., and Boman, P. G.: The Clinical and Pathological Identity of Pheochromocytoma: Report of a Case, J. A. M. A. **109**:1176 (Oct. 9) 1937.

NEOPLASMS OF THE PINEAL GLAND

Bailey, P., and Jelliffe, S. E.: Tumor of Pineal Body, Arch. Int. Med. **8**:851 (Dec.) 1911.

Dandy, W. E.: An Operation for the Removal of Pineal Tumors, Surg., Gynec. & Obst. **33**:113, 1921.

von Frankl-Hochwart, L.: Ueber Diagnose der Zirbeldrüsentumoren, Deutsche Ztschr. f. Nervenh. **37**:455, 1909.

Harris, W., and Cairns, H. W. B.: Diagnosis and Treatment of Pineal Tumors, Lancet **1**:3, 1932.

(*a*) Horrax, G.: Studies on the Pineal Gland: I. Experimental Observations, Arch. Int. Med. **17**:607 (May) 1916.

(*b*) II. Clinical Observations, ibid. **17**:627 (May) 1916.

Further Observations on Tumor of the Pineal Body, Arch. Neurol. & Psychiat. **35**:215 (Feb.) 1936.

——and Bailey, P.: Tumors of the Pineal Body, ibid. **13**:423 (April) 1925.

Pineal Pathology: Further Studies, ibid. **19**:394 (March) 1928.

Krabbe, K. H.: The Pineal Gland, Especially in Relation to the Problems of the Supposed Significance in Sexual Development, Endocrinology **7**:379, 1923.

Marburg, O.: Die Klinik der Zirbeldrüsenerkrankungen, Ergebn. d. inn. Med. u. Kinderh. **10**:146, 1913.

Van Wagenen, W. P.: A Surgical Approach for the Removal of Certain Pineal Tumors, Surg., Gynec. & Obst. **53**:216, 1931.

NEOPLASMS OF THE FLOOR OF THE THIRD VENTRICLE

Dods, L.: Adrenohypophyseal Dystrophies of Infancy and Childhood, M. J. Australia **2**:277, 1934.

Dorff, G. B., and Shapiro, L. M.: A Clinicopathologic Study of Sexual Precocity with Hydrocephalus, Am. J. Dis. Child. **53**:481 (Feb.) 1937.

Heuyer, G.; Lhermitte, J.; de Martel, and Vogt, C.: Un cas de macrogénitosome précoce liée à un épendymogliome de la région mamillo-tubérale, Rev. neurol. **2**:194, 1931.

Horrax, G., and Bailey, P.: Pineal Pathology, Arch. Neurol. & Psychiat. **19**:394 (March) 1928.

Le Marquand, H. S., and Russell, D. S.: A Case of Pubertas Praecox (Macrogenitosomia Praecox) in a Boy Associated with a Tumour in the Floor of the Third Ventricle, Roy. Berkshire Hosp. Rep., 1934-1935, p. 31.

Thomas, A., and Schaeffer, H.: Un cas de macrogenitosomie précoce avec hydrocéphalie, lesions inflammatoires de la région infundibulo-tubérienne et symphyse cervicale triméningée, sans néoplasme intracranien, Rev. neurol. **2**:595, 1931.

Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

THE CULTIVATION OF VACCINIA VIRUS IN DEEP COLUMNS OF MAITLAND MEDIUM. R. L. THOMPSON and M. S. COATES, J. Infect. Dis. **64**:105 (March-April) 1939.

Thompson and Coates found that increasing the oxygen tension in cultures by passing air through the medium did not enhance the growth of the virus, while decreasing the oxygen tension by excluding the air did enhance it. Multiplication of vaccine virus could easily be obtained in columns of Maitland medium up to 115 mm. in depth. The New York City Board of Health strain of vaccine virus was used and was carried through 25 serial transfers without any change of virulence.

TOOMEY, Cleveland.

THE NUTRITIVE REQUIREMENTS OF THE SALMONELLAS: I. TRYPTOPHANE AND THE GROWTH OF THE TYPHOID BACILLUS. W. BURROWS, J. Infect. Dis. **64**:145 (March-April) 1939.

Burrows found that the amino acid tryptophan is not essential to the growth of the typhoid bacillus even though this organism apparently requires it. They also found that, contrary to the usual belief, the typhoid bacillus produces indole in extremely small amounts.

TOOMEY, Cleveland.

Vitamins; Avitaminoses

CITRATES IN THE TREATMENT OF INFANTILE RICKETS. A. T. SHOHL and A. M. BUTLER, New England J. Med. **220**:515 (March 23) 1939.

Shohl and Butler report the results of the treatment of rickets in 2 Negro babies, 5 and 11 months old, respectively. Tables show for each patient the concentrations of serum calcium, inorganic phosphorus, phosphatase and protein, the rachitic changes as evidenced roentgenographically, the diet and the therapy during the period of study. The roentgenograms presented unmistakable evidence that healing of the rickets had been initiated and was progressing. However, both the roentgenograms and the concentrations of serum calcium and inorganic phosphorus showed that healing was not complete when the experimental study was interrupted. The amount of citrate given each patient daily corresponded approximately to that contained in five or six large oranges.

The authors believe that this new form of therapy not only offers an adjunct to accepted measures for the treatment of infantile rickets but may have application to other types of disorders of calcium and phosphorus metabolism.

GENGENBACH, Denver.

MEDICAL PROGRESS: THE WATER-SOLUBLE VITAMINS. A. P. MEIKLEJOHN, New England J. Med. **220**:518 (March 23) 1939.

Vitamin B Complex.—Thiamin has been regarded as the "antineuritic" or "antiberiberi" factor because it will cure animals of a disease which in some respects resembles human beriberi. Unusually good sources of this vitamin are pork, ham, liver, peanuts and dried brewers' yeast. A safe optimum allowance is between 1 and 2 mg. of thiamin daily. For underweight children with poor appetite, 3 teaspoonfuls daily of autolyzed yeast is recommended.

There has not yet been time to determine with certainty the distribution of nicotinic acid in foods. It is certainly present in yeast and crude liver extract. The daily oral administration of 500 mg. in five divided doses has been recommended as usually effective.

Clinically a deficiency of ascorbic acid results in scurvy. The best sources are fruit and fruit juices. A daily dose of 20 to 50 mg. should insure a liberal supply. In the treatment of scurvy large doses of the vitamin may be given (as much as 1 Gm. a day) by mouth. The administration of pure vitamin preparations is rarely sufficient for the complete cure of any deficiency disease and should never be considered as a substitute for a good general diet.

GENGENBACH, Denver.

EXOGENOUS AND ENDOGENOUS AVITAMINOSIS AND HYPOVITAMINOSIS: A STUDY OF RICKETS IN TWINS. J. R. DREYFUS, Jahrb. f. Kinderh. **147**:352 (Oct.) 1936.

One member of a pair of twins acquired severe rickets while her twin brother developed into a healthy child. Numerous instances of a similar nature are discussed. There is often an inherent inability to absorb vitamins even when they are given in more than sufficient amounts. Irradiation with ultraviolet rays is often unsuccessful, which suggests that the inability to utilize vitamins is general.

LANDAU, Hannibal, Mo.

EFFECT OF L-ASCORBIC ACID ON THE RETICULOENDOTHELIAL SYSTEM. S. TASAKA, Acta pædiat. japon. **45**:403 (March) 1939.

When a 5 per cent solution of l-ascorbic acid is injected either intravenously or subcutaneously into adult rabbits in doses of 2 cc. per kilogram of body weight there is a transient activation of the reticuloendothelial system, as tested by the Adler-Reimann congo red method. The effect, however, appears to diminish rapidly, so that at the end of twenty-four hours after the injections there is no evidence of reticuloendothelial stimulation.

KATO, Chicago.

Hygiene; Growth and Nutrition; Public Health

STUDIES REGARDING EARLY DEATH, ITS RELATIONSHIP TO SEX AND SELECTION: II. COMMUNICATION REGARDING PERINATAL DEATH—I. STILLBIRTHS. M. PFAUNDLER, Ztschr. f. Kinderh. **60**:467 (Feb. 18) 1939.

In a previous publication in this journal (Studies Regarding Early Death, Its Relationship to Sex and Selection: Regarding Order of Intrauterine Death, *Ztschr. f. Kinderh.* **57**:185, 1935) Pfaundler pointed out that the curve of intrauterine death drops sharply from a high embryofetal peak in the early months of pregnancy to the seventh or eighth month. At the peak the male sex is involved almost exclusively. There is a second perinatal peak of fetal mortality, with which this article is concerned.

The article does not lend itself well to abstracting, because of its length and detail. The difficulties in determining the time relation of death to birth are discussed. The interrelationship of causes is presented schematically. A combination of causes is common. Figures of various authors are compared. Pfaundler proposes separation of causes of stillbirth into two main groups: (1) obstetric mechanical causes (betabasic) and (2) causes of death preceding birth (ametabasic). Ametabasic causes are distributed evenly over the last three months of pregnancy. Metabasic causes are mainly responsible for the perinatal peak. Both classes of causes affect the male sex predominantly, but the metabasic class much more so. The assumption that the larger size of the male fetus is responsible is erroneous. Apparently the male is less resistant. In contrast to what is observed of all other stillbirths, those due to malformations, according to extensive American statistics, involve mainly the female sex.

SIEMSEN, Chicago.

COMMUTING SCHOOL PUPILS. U. HJÄRNE, Svenska läk.-tidning. **35**:22 (Jan. 7) 1938.

Hjärne criticizes the increasing tendency in Sweden for school children living in the country outside cities to travel by train or bus to and from school every day instead of being taken care of and living in the city during the school year. Such traveling school children suffer from too short a period of sleep and have less time for outdoor play than other children, and their meals, especially their morning meals, are unsatisfactory. WALLGREN, Göteborg, Sweden.

Prematurity and Congenital Deformities

FOOD HABITS OF MOTHERS OF MALFORMED CHILDREN. D. P. MURPHY and A. D. BOWES, Am. J. Obst. & Gynec. **37**:460 (March) 1939.

Information about the regular food habits of 545 mothers who had given birth to malformed children was obtained, and the following facts were noted as significant:

About 35 per cent of these women took no milk during pregnancy. About 20 per cent took 1 quart (945 cc.) or more of milk daily. About 20 per cent had two servings daily of leafy vegetables, and only 10 per cent reported having from two to four servings daily of other vegetables. Citrus fruits were taken once daily by 18 per cent, and 13 per cent had two servings of other fruit daily. About 25 per cent used too much bread, and only 17 per cent used whole grain bread regularly or often. Excessive use of coffee, tea or alcoholic beverages was not indicated. Approximately 40 per cent had an inadequate diet when pregnant with their malformed children. Anemia was twice as frequent in those mothers whose diets were inadequate. Anemia occurred in the women who gave birth to congenitally malformed children four times as often as in a control series. The observations offer no proof that an inadequate diet or that anemia is a predisposing factor in the occurrence of congenital malformations. However, both characteristics were observed with unusual frequency. ARENA, Durham, N. C.

ARACHNODACTYLY: ITS OCCURRENCE IN SEVERAL MEMBERS OF ONE FAMILY. J. HARRISON and M. J. KLAINER, New England J. Med. **220**:621 (April 13) 1939.

Marfan first called attention to long slender fingers and toes with a tendency toward clawing. Harrison and Klainer report the case of a 6 year old girl who was a blue baby at birth. She had contracture of the fingers at one month and a heart murmur, pigeon breast and dorsolumbar scoliosis at 6 months. At 6 years she was 44½ inches (113 cm.) tall and weighed only 33 pounds (15 Kg.); her skull was dolichocephalic; there were marked asymmetry of the sternum and deformity of the spine; there was practically no subcutaneous fat, and the musculature was poor; the fingers and toes were long and slender, with clawing; there was clubbing of the fingers and cyanosis of the nails; the ears and teeth were irregular; the palatal arch was high; a prolonged murmur was heard all over the precordium; the pupils were sluggish to light, and there was deep physiologic cupping of the disks.

The mother, mother's brother, patient's brother and cousin showed varying degrees of arachnodactyly. GENGENBACH, Denver.

ABDOMINAL PREGNANCY WITH A FULL TIME LIVING CHILD. I. C. HAINS, M. J. Australia **1**:268 (Feb. 18) 1939.

Hains reports a case as described in the title. The placenta was twice the normal size. It rose from a broad band like the pedicle of some ovarian cysts,

from the top of the right broad ligament, and had a huge blood supply. It had amniotic membrane on one surface and chorionic membrane on the other.

GONCE, Madison, Wis.

FOETUS AMORPHUS. I. BRODSKY, M. J. Australia **1**:539 (April 8) 1939.

Brodsky presents a detailed description of foetus amorphus.

GONCE, Madison, Wis.

HEREDITARY BRACHYDACTYLY. E. TAGE-HANSEN, Hospitalstid. **81**:284 (March 22) 1938.

Tage-Hansen reports the incidence of brachydactyly in six generations of a family. In the last three generations 14 members were found to have the anomaly. The hereditary factor is dominant. The following other congenital malformations occurred among the 60 remaining brachydactyly-free members of the family: polydactyly in 1, congenital luxation of the hip joint in 2 and harelip in 2.

WALLGREN, Göteborg, Sweden.

A CASE OF DYSOSTOSIS CRANIOFACIALIS (CROUZON). A. SUNDAL, Norsk mag. f. lægevidensk. **99**:445 (April) 1938.

Sundal reports craniofacial dysostosis in a diabetic girl of 11 years with satisfactory mental development and with healthy parents and sisters. The principal signs of her malformation were: oxycephaly, exophthalmos with the eyes widely separated, divergent strabismus, coloboma iridis and great impairment of the sight of the right eye. There was no papillitis.

WALLGREN, Göteborg, Sweden.

A CASE OF CHONDRODYSTROPHY. T. THYSELL, Svenska läk.-tidning. **35**:869 (June 10) 1938.

Typical chondrodystrophy was encountered in a girl of 2½ years. No hereditary factor was found. The intelligence quotient was normal.

WALLGREN, Göteborg, Sweden.

A CASE OF HEMISACRUM. M. C. M. OLTMANS-SMID, Maandschr. v. kindergeneesk. **8**:239 (March) 1939.

This is a description of the case of a girl of 2 years who had hemisacrum. She was troubled with disturbances of defecation and urination, which were probably caused by a congenital lesion of the spinal cord (myelocyst).

VAN CREVELD, Amsterdam, Netherlands.

Newborn

BIRTH INJURIES OF THE CORNEA AND ALLIED CONDITIONS. R. I. LLOYD, Am. J. Ophth. **21**:359 (Nov.) 1939.

Lloyd discusses the genesis of injuries of the cornea incurred at birth and the different types. He reports 6 cases, in all of which the left eye was the one affected. This is to be expected because of the preponderance of left occiput anterior presentations which bring the left eye to the rear. Pigmentation of the posterior corneal and anterior lenticular surfaces is explained by late separation of the cornea from the tunica vasculosa lentis. This may in turn be the result of delayed formation of the anterior chamber and should direct one's attention to buphthalmos.

W. S. REESE. [ARCH. OPHTH.]

AN OUTBREAK OF INFECTIOUS DIARRHEA AMONG NEWBORN INFANTS. A. M. KIMBERLY, New England J. Med. **220**:664 (April 20) 1939.

Six cases of infectious diarrhea arose directly following the admission to a hospital ward of an infant who had been discharged six days before from a hospital in New York. Five of the six babies who acquired the disease succumbed to it. Three of the babies were examined post mortem, and all 3 showed parenchymatous degeneration of the liver, kidneys and heart, with fatty degeneration of the liver. Two showed edema of the lungs, with aspiration bronchitis from foreign material. One showed, besides peritonitis, bilateral empyema and the congenital anomalies of cleft palate and left harelip, right cryptorchidism and Meckel's diverticulum. The gastrointestinal disturbances were very mild, with no ulcerations or areas of hemorrhage.

GENGENBACH, Denver.

NUCLEAR JAUNDICE IN ICTERUS FAMILIARIS. C. DE LANGE, Maandschr. v. kindergeneesk. **8**:257 (April) 1939.

In a case of severe jaundice some of the classic features of icterus gravis familiaris were lacking (absence of erythroblastemia on the third day of life and absence of erythroblastosis in the liver, spleen and kidney), yet the presence of nuclear jaundice of the brain and the absence of any obstruction in the bile ducts confirmed the diagnosis.

VAN CREVELD, Amsterdam, Netherlands.

SCLEREMA ADIPOSUM NEONATORUM. C. GOEDHART, Maandschr. v. kindergeneesk. **8**:281 (April) 1939.

Goedhart describes histologic changes in the skin of a baby suffering from "sclerema adiposum." In the cutis and subcutis streptococci were abundant, especially in the lymph vessels. Many capillaries were distended and filled with blood. The greatest changes—among others, "necrosis"—were round the adipose tissue, so that the impression gained was that the streptococcic toxins had caused special changes in this tissue and in this way the hardness of the skin. On the right cheek the child showed an infection looking like a mosquito bite. The mother had latent syphilis with positive blood reactions. No signs of syphilis and no spirochetes were found in the child, not even in the organs. A second patient, a child, died within three days from streptococcic sepsis.

VAN CREVELD, Amsterdam, Netherlands.

Acute Contagious Diseases

WASHING OF HAEMOPHILUS PERTUSSIS VACCINES. J. A. TOOMEY and W. S. TAKACS, J. Infect. Dis. **64**:89 (Jan.-Feb.) 1939.

"Freshly isolated pertussis organisms washed once in distilled water lose none of their original morphologic characteristics and virulence. There is a slight loss in their ability to produce agglutinins which is well within the range of experimental error.

"The morphology of these organisms when frequently washed in distilled water does not change. They become completely avirulent, although their ability to produce agglutinins is retained.

"The methods employed to prepare vaccines do not explain the divergent results obtained by the various workers quoted."

FROM AUTHORS' SUMMARY (TOOMEY, Cleveland).

SIGNIFICANCE OF THE CONDITIONS OF EXPOSURE IN THE STUDY OF MEASLES PROPHYLAXIS: AN ADDED CRITERION IN THE EVALUATION OF MEASLES PROPHYLACTIC AGENTS. S. KARELITZ and R. F. KARELITZ, J. Pediat. **13**:195 (Aug.) 1938.

There has been considerable difference of opinion in the literature as to the value of the various substances used in the prophylaxis of measles. The authors believe that much of this difference in opinion may be accounted for by the failure to consider the conditions under which the exposure of the susceptible subjects was assumed to have occurred.

This report deals with results obtained in 314 children treated prophylactically with various placental extracts and with globulin of immune adult serum. The results have been analyzed according to the type and duration of the exposure. The following conclusions are drawn: 1. The dose of virus or the frequency of infection within a given time or the intimacy or duration of the exposure to the disease determines in large measure both the rate of incidence of measles and the efficacy of a given dose of any substance prophylactic against this disease. 2. The wards of hospitals and institutions are usually inadequate for the evaluation of a substance prophylactic against measles because of the uncertainty and difference of the intensity and duration of the exposure of the susceptible children. 3. Exposures presumably consummated in nurseries, at school, in busses, in playgrounds and at parties are no more certain than those in hospitals. 4. The percentage of completely protected children in homes varies with the hygiene, the greater number of protections being recorded for homes in which facilities make possible isolation of the sick child at an early stage of the disease. 5. The percentage of completely protected children in homes with poor hygiene increases progressively with a corresponding increase in the serum dose or potency. 6. The criteria for determining the dosage of a given preparation in the prophylaxis of measles should be modified to include the type or the condition of the exposure.

RAUH, Cincinnati.

SUPPURATIVE PAROTITIS AS A COMPLICATION OF MUMPS. E. C. PERLMAN, Minnesota Med. **21**:649 (Sept.) 1938.

Perlman has found that in most of the current textbooks little mention is made of suppuration in the parotid gland. The differential diagnosis between the suppurative and the epidemic type is definite and suggests that one never occurs with the other. He reports that suppurative parotitis occurs more than rarely as a sequel to operative procedures, notably those for suppurative abdominal conditions and also as a sequel to infectious diseases, such as typhoid fever, scarlet fever, diphtheria and pneumonia. He has found, however, that suppurative parotitis occurs as a complication of epidemic mumps, as is shown in a few case reports throughout the literature. He cites 6 such reports and himself describes a case of an 11 year old girl in whom epidemic parotitis of the left side was uneventful to the evening of the fourth day, when she began to complain of excessive pain over the right parotid gland and to have a temperature of 103.8 F., taken by mouth. This patient was given supportive treatment at home, and on the ninth day the abscess ruptured into the anterior wall of the external auditory canal, with profuse discharge of purulent material from the aural canal and definite fluctuation of the abscess below the ear. She was hospitalized and treated with hot packs for twenty-four hours to localize the suppuration, and the abscess was incised. Forty cubic centimeters of greenish yellow pus was evacuated and showed pure Staphylococcus aureus on culture. Two days later another fluctuant area below the incision was emptied by blunt dissection through the previous incision. After a convalescence of ten days, uneventful except for profuse draining, the patient was discharged. After a month there was complete closure of the wound, with a normally functioning parotid gland, and all symptoms had disappeared.

ANDERSON, Minneapolis.

ADVANCES IN THE PREVENTION AND TREATMENT OF CONTAGIOUS DISEASES OF CHILDHOOD. E. S. PLATOU and P. F. DWAN, Minnesota Med. **22**:71 (Feb.) 1939.

Platou and Dwan point out that statistics of mortality in Minnesota show a decided decline in the figures for deaths from the more common diseases of childhood since 1915 but that allocation of mortality by age groups reveals that the figures for deaths from diphtheria, scarlet fever, measles and pertussis have remained practically unchanged during that period. The authors feel that, although publicity has been given to immunization, hygiene, early diagnosis and treatment of contagious diseases in the schools, too little has been done regarding specific protection in early life. A condensed survey of the accumulated data on the following diseases is given: diphtheria, scarlet fever, measles, pertussis, erysipelas, meningitis, smallpox, rabies and tetanus.

ANDERSON, Minneapolis.

USE OF SULFANILAMIDE IN SCARLET FEVER. C. WESSELHOEFT and E. C. SMITH, New England J. Med. **219**:947 (Dec. 15) 1938.

The authors' conclusions are:

"Sulfanilamide therapy of scarlet fever in the eruptive stage in the usual dosage . . . does not reduce the toxicity as manifested by the intensity of the eruption or the duration of the fever.

"Sulfanilamide therapy has not reduced the incidence of complications in a compilation of three series of observations. . . .

"Sulfanilamide therapy appears to be useful in certain infections of the mastoid cells, but the possibility of an associated infection of the blood stream through destruction of bone may be a factor.

"Infections of the blood stream and meningitis are indications for sulfanilamide therapy. In these two complications, the results of its administration have lowered the mortality.

"Bacteriological evidence suggests that the use of sulfanilamide in the last week of convalescence does not reduce the carrier rate through eradication of hemolytic streptococci from the nose and throat.

"The use of sulfanilamide as a prophylactic in non-immune contacts is a problem for carefully controlled investigations."

GENGENBACH, Denver.

PHENOMENA OF ALLERGY AND ANERGY DURING THE COURSE OF SCARLET FEVER IN CHILDREN INOCULATED AGAINST THIS DISEASE. M. DE BIEHLER, Bull. Soc. pédiat. de Paris **36**:593 (Oct.) 1938.

In 19 children who had received inoculations against scarlet fever a redder area was observed at the site of previous inoculation when they contracted the disease later. This is interpreted as a manifestation of allergy. In 11 there was a blanched spot at the site of previous inoculation. This was interpreted as evidence of local antitoxic immunity and temporary disappearance of allergy. Those in the latter group had the disease in milder form than those in the former, who showed more fever, and among whom 2 cases of nephritis and 1 of otitis media developed.

BENJAMIN, Montreal.

INFLUENCE OF RUBEOLA ON ALLERGY TO TUBERCULIN. G. BLECHMANN and R. H. FRANÇOIS, Bull. Soc. pédiat. de Paris **36**:595 (Oct.) 1938.

A girl 6 years old received a tuberculin test during the period of incubation of rubeola. The reaction did not become positive until about two weeks later. A month later another intradermal injection, with use of a weaker dilution of tuberculin, as well as a scratch test produced positive results after forty-eight hours.

BENJAMIN, Montreal.

NERVOUS COMPLICATIONS OF CHICKENPOX. M. PREBIL, Med. ital. **1**:2 (Jan.) 1939.

Meningoencephalitis following chickenpox in an 8 year old child is described. The onset of the complication occurred eight days after the onset of the chickenpox. The child recovered at the end of three weeks. The theories as to the genesis of nervous complications in the exanthems are discussed. The nervous complications are placed in fourteen groups depending on localization. Cases from the literature are mentioned in connection with these fourteen groups. The diagnosis and prognosis are discussed. The cerebellar complications give the best prognosis; the myelitic and the ocular syndromes give the poorest.

MARTOCCIO, Brooklyn.

IMPORTANCE OF TYPES OF DIPHTHERIA BACILLI FOR CLINICAL STUDY OF THE DISEASE. W. HILGERS and F. THOENES, Jahrb. f. Kinderh. **147**:339 (Oct.) 1936.

The method of differentiating diphtheria bacilli by the tellurite method (potassium tellurite) was tried. It was found to be of little or no practical importance, as Diphtheria mitis was found to be the causative agent in many cases in which the disease was severe, while Diphtheria gravis was frequently found in cases in which the disease was mild.

LANDAU, Hannibal, Mo.

ACUTE INFECTIOUS DISEASES IN EARLY INFANCY. H. ZISCHINSKY, Jahrb. f. Kinderh. **148**:2 (Nov.) 1936.

An extensive review of the literature is given. After this the author's own material is presented. One case of measles in a child of 3 weeks is recorded. From that age on up to the age of 12 months (the limit considered in this study) the incidence of this disease was progressive. The mortality in the first quarter of the year was 47.8 per cent, in the second 34.8 per cent, in the third 41.5 per cent and in the fourth 31 per cent. The exanthem was often atypical. Koplik spots were frequently absent. One of the forms frequently seen in early childhood was the toxic type, characterized by signs of circulatory disturbance, unrest, delirium and convulsions. Purulent bronchitis was often present. Another type was characterized by pulmonary symptoms, with signs of intoxication, and the exanthem was not so prominent.

Pulmonary complications were most prominent. Otitis, enteritis, pyoderma, stomatitis and septicemia are reported among the complications.

The younger the child the poorer was the prognosis.

Rubeola was also atypical. Often it was impossible to make the diagnosis with certainty. Two forms are described, the morbilliform and the scarlatinal. The only fatalities occurred in cases complicated by pneumonia or enteritis.

Other diseases will be considered in a future article.

LANDAU, Hannibal, Mo.

MEASLES; EXANTHEMA SUBITUM. H. OPITZ, Kinderärztl. Praxis **10**:6 (Jan.) 1939.

Opitz discusses the differential diagnosis between measles, exanthema subitum and German measles on the basis of 1 of his own cases. His etiologic conception of exanthema subitum is interesting, inasmuch as he shares the opinion of Hainiss, Kleinschmidt and Rietschel, according to which this disease is identical with a toxic rash due to grip, in contradistinction to the theory held by Glanzmann, who believes that exanthema subitum is a disease entity with a specific cause. Opitz never saw the disease spread in a ward when it suddenly occurred.

HEYMANN, Cleveland.

EXPERIENCES WITH DIPHTHERIA CARRIERS. H. MENNEKAS, Med. Klin. **35**:49 (Jan. 13) 1939.

Mennekas found antiseptic solutions valueless in eliminating diphtheria bacilli from the nose and throat. Fever therapy may prove to be of value. It is important to create healthy conditions in the mouth and nose. Carious teeth and hypertrophied adenoids should be removed.

SIEMSEN, Chicago.

FURTHER CASES OF SPONTANEOUS POLIOMYELITIS IN DOMESTIC ANIMALS (HOGS). E. FRAUCHIGER and W. MESSERLI, Schweiz. med. Wchnschr. **69**:74 (Jan. 28) 1939.

Frauchiger and Messerli say that since acute anterior poliomyelitis has been observed in cattle they have given special attention to paralytic symptoms in domestic animals. In this report they describe observations on 2 hogs which presented symptoms that greatly resembled those of acute anterior poliomyelitis. On the basis of these symptoms the disorder was diagnosed as probable poliomyelitis. Both animals were killed, and microscopic examination of the spinal cords revealed in both histologic appearances resembling those of acute anterior poliomyelitis in human subjects. Material from the spinal cords of these animals was introduced into 2 other hogs and 1 steer. Because of an inadequate technic, nothing could be learned from the inoculation test on the hogs, but in the case of the steer, with which a formerly devised technic was employed for the inoculation, fever developed, the curve of which showed the dromedary type. Other symptoms included signs of fatigue, stiffness of the neck and an ataxic gait. From the seventh day after the inoculation the symptoms commenced to subside, and a few days later the animal seemed normal again. The animal was killed fourteen days after the inoculation. The histologic appearances of the central nervous system were those of lymphocytic meningoencephalomyelitis rather than those characteristic of poliomyelitis, but it must be remembered that the animal was not killed during the acute stage, when signs more typical of poliomyelitis might have been detected. However, since Spielmeyer's investigations demonstrated that similar histologic appearances do not necessarily indicate the same disease or causal agent, the authors do not definitely conclude that the described paralytic symptoms in hogs are identical with those in human poliomyelitis, but they believe that this may be the case. They think that the detection of poliomyelitis in further animals and the transmission of the disease from animal to animal and from man to animal will provide more certainty.

J. A. M. A.

DOES SCHOOL ATTENDANCE INCREASE THE DIPHTHERIA EXPECTANCY? AN EPIDEMIOLOGIC "INDEX OF DEVIATION FROM INCIDENCE EXPECTANCY." B. DE RUDDER and K. DITZEN, Ztschr. f. Kinderh. **60**:495 (Feb. 18) 1939.

Using the index mentioned in the title, de Rudder and Ditzen studied the relation between school attendance and diphtheria incidence during the years 1928 to 1939. Apparently school attendance is of less importance in the incidence of diphtheria than is a seasonal epidemiologic increase. This contention was substantiated by a comparison of the incidence during school months and vacation months in which it was shown that the figures fell within the minimum of the incidence curve.

SIEMSEN, Chicago.

IS NONPROTEIN NITROGEN INCREASE AN ADDITIONAL PROGNOSTIC SIGN IN DIPHTHERIA? BENNHOLDT-THOMSEN and R. DIECKERHOFF, Ztschr. f. Kinderh. **60**:565 (Feb. 18) 1939.

The views regarding the prognostic value of an increase in nonprotein nitrogen in diphtheria vary. The authors report their findings in 160 cases. In general, the more severe the disease the higher are the values during the first fifteen days of

illness, and the greater the increase above 35 mg. per hundred cubic centimeters the higher the mortality. Further, the curve of values during the course of illness is important, an incline in the curve indicating an unfavorable, decline a favorable, prognosis.

SIEMSEN, Chicago.

CONVALESCENT SERUMS AND THEIR USE IN THE TREATMENT OF INFECTIOUS DISEASES. J. PROCHAZKA, Časop. lék. česk. **76**:37 (Jan. 15) 1937.

Measles convalescent serum has been ineffective in some localities because the serum was collected from patients with a toxic rash and not measles, because the serum was collected later than ten days after recession of the fever and because an increased dose (40 to 60 cc.) was not given to patients after the fifth day of incubation. Immune globulin was used therapeutically, with a shortening of the period of exanthem and a rapid return of the temperature to normal. Immune globulin was not used prophylactically. The disadvantages of horse serum scarlet fever antitoxin and the advantages of convalescent scarlet fever serum, especially as a prophylactic, are discussed. Of 25 children immunized with convalescent scarlet fever serum (10 cc.), a sore throat developed in only 1 in twenty-four hours, but this rapidly disappeared after injection of an additional 30 cc. of serum. In the treatment of several children with poliomyelitis convalescent serum was used intraspinally together with methenamine, so that the evaluation of the good result is not definite. In a small series of patients with mumps definite improvement was noted with the use of convalescent serum.

STULIK, Chicago.

ACTION OF CONVALESCENT SERUM ON THE FORMATION OF SPECIFIC SCARLET FEVER ANTIBODIES. P. ERHART, Časop. lék. česk. **76**:182 (Feb. 12) 1937.

Erhart cites the work of Neuber, who states that patients with erysipelas and scarlet fever when treated with convalescent serum do not acquire active immunity. This does not hold for measles. Using the Schultz-Charlton blanching method, he tested serums from patients treated with convalescent (scarlet) serum and serums from patients not treated with convalescent serum on alternate patients in a series of 64. In 13 of those tested with serums from patients not treated with serum there was a more potent reaction, while in 19 of those tested with serums from the serum-treated patients there was a more potent reaction, i. e., practically the same result. In a second series a pool of serums from 30 patients not treated with serum was checked against a pool of serums from 14 serum-treated patients with the following result: Of 34 subjects tested on both arms, 22 had stronger blanching on the "serum-treated" test arm, 7 had an equal reaction on both arms and only 5 had stronger blanching on the "serum-untreated" test arm. The author feels that he was unable to verify the statement that convalescent serum inhibits the formation of scarlet fever antibodies.

STULIK, Chicago.

THE 2,6-DICHLOROPHENOLINDOPHENOL-REDUCING POWER OF THE URINE OF PATIENTS WITH MEASLES. K. KAWASHIMA and I. GAMMO, Acta pædiat. japon. **45**:245 (Feb.) 1939.

Urine obtained in the early febrile stage of measles exhibited pronounced reducing power to 2,6-dichlorphenolindophenol, but there was no correlation to the amount of urinary cystine or to the degree of fever.

KATO, Chicago.

PREPARATION AND CLINICAL USE OF BACILLUS PERTUSSIS VACCINE. J. P. WU, F. T. CHU and C. L. TSAO, Chinese M. J. **54**:517 (Dec.) 1938.

A positive culture was usually obtained when a properly prepared cough plate was exposed during the first two or three weeks of the disease. The preparation of the medium and the handling of the cough plate are described. The character-

istics of the fresh organisms showed that all strains belong to phase I of Leslie—Gardener's classification. Both sheep blood and human blood are effective in preserving the antigenic properties of the organisms. Tests show that the vaccine prepared from the authors' fresh culture was agglutinable by the antipertussis rabbit serum to the full titer of the serum. This was also true of Sauer's vaccine. Both were capable of stimulating antibody formation (in rabbits) by way of successive intravenous inoculations at short intervals.

Injected into children aged 5 months to 5 years, the vaccines produced no untoward effect, and in the blood of these vaccinated children specific agglutinin was regularly demonstrated. NEFF, Kansas City, Mo.

BETA HEMOLYTIC STREPTOCOCCUS: I. THE TECHNIC OF SEROLOGICAL CLASSIFICATION (GRIFFITH). II. SEROLOGICAL TYPES ISOLATED FROM SCARLET FEVER PATIENTS AND THEIR CONTACTS. C. J. WU and R. H. P. SIA, Chinese M. J. **55**:146 (Feb.) 1939.

I. If the serologic test is made with strong agglutinating serums, a type-specific agglutination will occur almost at once when the proper immune serum is mixed with the bacterial suspension on the slide. An immediate reading of the result is advised when a classification of beta hemolytic streptococci is attempted.

II. An attempt to classify organisms from patients with scarlet fever and contacts is described. The work of others is confirmed as to scarlet fever being caused by multiple types of hemolytic streptococci. The same type is usually found in other members of the family, whether patients or contacts. Serologic typing is useful in studying the epidemiology. NEFF, Kansas City, Mo.

A NEW METHOD OF IMMUNIZATION FOR WHOOPING COUGH. T. OTANI, Orient. J. Dis. Infants. **25**:43 (Jan.) 1939.

Basing his work on the possibility of producing immunity against Bordet-Gengou bacilli by introducing living organisms of low toxicity, Otani cultivated the bacilli through many generations on nutrient mediums containing proper amounts of vitamin C. This vitamin, in numerous experiments, was observed to exert a decided detoxicating influence on the bacilli of whooping cough. By a combination of subcutaneous injection and tracheal instillation monkeys were adequately protected from severe infection when exposed to the disease in a typical form or when inoculated with living organisms. KATO, Chicago.

ANTERIOR POLIOMYELITIS TWICE IN THE SAME PERSON. O. J. NIELSEN, Hospitalstid. **81**:333 (April 5) 1938.

A 9 month old boy fell ill with fever and paralysis of the legs. The paralysis decreased gradually. At the age of 12 he was examined at an orthopedic clinic and was found to have flaccid paresis of several of the muscles in both legs, predominantly in the left one, with double pes valgus. Postpoliomyelitic paresis was diagnosed. At 30 years of age he again fell ill with fever, stiffness of the neck, pains in the legs, paralysis of the legs and of the abdominal and gluteal muscles, urinary retention and pleocytosis of the spinal fluid. He recovered, and the paralysis decreased gradually until it was of about the same extent and severity as before the last attack. This is the fifteenth instance of a second attack of poliomyelitis in the same person. WALLGREN, Göteborg, Sweden.

POLIOMYELITIS. P. M. HOLST, Norsk mag. f. lægevidensk. **99**:94 (Jan.) 1938.

During the 1936 epidemic of poliomyelitis about 900 cases were reported in Norway, 67 of which occurred in Oslo. Abortive cases seemed to be frequent in rural districts but were rare in the capital. During the epidemic the period of

isolation was changed from three to six weeks, though no valid reason could be given for this procedure. In 44 cases the treatment was by convalescent serum; no effect could be demonstrated either in the preparalytic stage or later. In 3 cases, in all of which the disease ended fatally, treatment was by respirator.

WALLGREN, Göteborg, Sweden.

ADDIS' COUNT IN SCARLET FEVER. T. Bjering, Ugesk. f. læger **100**:342 (March 31) 1938.

Sixteen children suffering from scarlet fever were examined by Addis' method of determining the amount of cell elements and casts in the urine. The tests were made every second day during the stay at the hospital. In 2 of the children typical scarlatinal hemorrhagic nephritis developed. The other children had normal urinary findings.

WALLGREN, Göteborg, Sweden.

MENINGOCOCCIC MENINGITIS TREATED WITH SULFANILAMIDE. A. ELDAHL, Ugesk. f. læger **100**:365 (April 7) 1938.

Twelve children, 7 of whom were less than 1 year of age, were treated with intraspinal and intramuscular injections of an aqueous 0.8 per cent solution of sulfanilamide. The doses were 5 to 30 cc. daily for the intraspinal and 35 to 150 cc. daily for the intramuscular injections. Nine of the children recovered. Previously the average death rate from meningococcic meningitis in children of the same age group was 70 per cent.

WALLGREN, Göteborg, Sweden.

CASES OF HEINE-MEDIN DISEASE. H. BROEKEMA, Maandschr. v. kindergeneesk. **8**:193 (Feb.) 1939.

During the epidemic of poliomyelitis which occurred in Holland in 1938, 70 patients were observed in Leyden and its environs. Only 2 of the 70 patients had convulsions; 7 had the dromedary type of fever curve. Four patients were ascertained to have been in contact with other persons who had poliomyelitis; most probably the number with abortive poliomyelitis had been fairly large.

Of the 70 patients, 57 showed paralysis, and 9 of them died shortly after their arrival at the hospital. Though always some form of therapy was applied immediately, the disease was progressive in 9 patients. Therapy consisted in the injection of serum of convalescents, blood transfusion, giving of methenamine (urotropin) orally and intralumbar injections of vitamin B_1. The results of the therapy after a stay in the hospital of six weeks are compared. Eighteen patients were treated with vitamin B_1, and they showed a quicker recovery than the 14 patients who were treated without this vitamin.

VAN CREVELD, Amsterdam, Netherlands.

Acute Infectious Diseases

CHRONIC BRUCELLOSIS (UNDULANT FEVER): AN ANALYTICAL STUDY OF THE POSITIVE REACTORS AMONG SCHOOL CHILDREN. F. E. ANGLE and W. H. ALGIE, Ann. Int. Med. **12**:1189 (Feb.) 1939.

Grade school and high school children of Kansas City, Kan., were tested. Evidence of chronic illness was found in 38.7 per cent of 462 positive reactors to brucellergin in 1937. Persistence of symptoms was noted in 57.5 per cent in 1938. Control studies indicated that the incidence of chronic illness was greater in the group under investigation.

The ambulatory and subclinical types of brucella infection are apparently not uncommon.

READING, Galveston, Texas.

A CHARACTERISTIC SYNDROME DUE TO INFLUENZA BACILLI. H. KLEINSCHMIDT, Kinderärztl. Praxis **10**:53 (Feb.) 1939.

Kleinschmidt describes a new and characteristic syndrome due to infection with influenza bacilli. He refers to 2 of his own and to several similar cases which were found reported in the literature. The start of this disease is overshadowed by stenosis of the larynx, which usually leads to a wrong diagnosis of diphtheria or of a foreign body. Croupy symptoms generally improve soon. Purulent pericarditis then becomes evident; the pus obtained shows influenza bacilli. Pneumonia with or without empyema is always present. The outcome ultimately depends on whether or not influenzal meningitis develops. Kleinschmidt believes that this represents a syndrome which takes its origin from a throat infection with influenza bacilli and progresses through the mediastinum into the cavity of the thorax. Infection of the blood stream does not necessarily have to be assumed, in spite of the presence of pericarditis, inasmuch as patients have been observed in whom meningitis did not develop and who ultimately recovered completely.

HEYMANN, Cleveland.

RELAPSING FEVER—CLINICAL AND STATISTICAL STUDY OF THREE HUNDRED AND THIRTY-SEVEN CASES. H. L. CHUNG and F. C. CHANG, Chinese M. J. **55**:6 (Jan.) 1939.

No particular age group is immune to relapsing fever, but persons under 10 and those above 60 years of age are much less frequently involved. Only 3 per cent of the authors' patients were under 10 years of age. A sudden rise of the incidence is found in the group from 10 to 19 years of age, in which the percentage is 11. One patient was under 1 year of age. The immunity of young children is due to their absence from army camps, poorhouses and small inns in the slums, where epidemics are most apt to occur, the occurrence being favored by the multiplication and migration of body lice from one person to another. Even physicians and nurses in exercising their clinical duty among the sick occasionally acquire infected body lice.

In children it sometimes happens that the fever has an irregular course opposite to that described in textbooks, permitting the diagnosis to be overlooked unless there is routine examination of the blood for spirochetes. The routine treatment included careful delousing and intravenous injections of neoarsphenamine, which caused disappearance of the fever in four to forty-eight hours. Usually there is a sudden crisis within the first six hours. The authors discuss the difficulty of distinguishing between a relapse and a reinfection. More knowledge is needed on the subject of immunity. In the treatment of a relapse or a reinfection the dose used was below 10 mg. per kilogram of body weight but was approximately one-half more than this for 2 patients in whom relapse occurred while they were in the hospital. Of 21 patients who died only 13 had been given specific treatment before death, and some of these were dying at the time of admission. The gravest complications were bacteremia and pneumonia, and these were usually the immediate cause of death.

NEFF, Kansas City, Mo.

CASES OF GAS PHLEGMON. F. KOCH, Hygiea **100**:194 (March 31) 1938.

Koch reports on 24 patients with gas phlegmon treated at the university clinic in Lund, Sweden. The series included 2 boys, 6 and 9 years of age, in whom the disease developed after severe traumatic lesions. For both patients amputation of the affected limb had to be done, after which the 9 year old boy died, while the younger boy recovered.

WALLGREN, Göteborg, Sweden.

AN EPIDEMIC OF TULAREMIA IN SWEDEN. G. OLIN, Hygiea **100**:236 (April 15) 1938.

In Sweden 200 cases of tularemia have occurred during recent years, 115 of which occurred in a small district in the eastern part of the country. Among those infected 5 were children below 9 years of age and 15 children between 10 and 19 years. In most instances the disease was of the ulceroglandular type; only exceptionally was it of the typhoid, glandular or oculoglandular type. Recovery occurred in all cases. The disease is supposed to have been transmitted in most instances by mosquitoes.

WALLGREN, Göteborg, Sweden.

ANEMIA WITH RHEUMATIC FEVER. G. GEZELIUS, Svenska läk.-tidning. **35**:873 (June 10) 1938.

Attention is called to the anemia accompanying rheumatic fever and to the correlation that exists between the degree of anemia and the severity of the rheumatic disease. The red blood cell picture is valuable in studying the course of the disease and should be employed in connection with the sedimentation test. The article is illustrated with reports of 5 instructive cases.

WALLGREN, Göteborg, Sweden.

TWO PAIRS OF SIBLINGS WITH TYPHOBACILLOSIS. G. VON SYDOW, Svenska läk.-tidning. **35**:878 (June 10) 1938.

1. A girl of 12 years and her brother of 9 years were exposed to tuberculous contagion Dec. 23, 1936, and Jan 6, 1937. On Jan. 24, both children fell ill with high fever, which lasted for four weeks, then gradually disappeared. It was accompanied by erythema nodosum. The tuberculin test was positive. Roentgen examination showed pulmonary changes. The girl recovered, but the boy again became feverish, miliary tuberculosis developed, and he died May 14.

2. A boy of 8 and his sister of 6 years were exposed to tuberculous infection on Dec. 31, 1936. The boy fell ill with high fever on February 6 and the girl the next day. Their fever was high during some weeks, then gradually fell, and they were fever free within four to six weeks after the beginning of the disease. During the period of fever the tuberculin test was positive, and hilar changes were demonstrable. Later on the boy acquired pleurisy. Both recovered.

WALLGREN, Göteborg, Sweden.

PAUL AND BUNNELL TEST. H. BEEUWKES, Nederl. tijdschr. v. geneesk. **83**:149 (Jan. 14) 1939.

In view of a high agglutination titer for sheep erythrocytes found for serums originating from patients with malaria, a control investigation was made on a number of serums from patients not suffering from glandular fever. A titer of over 1:512 has some value as a complementary diagnostic sign of glandular fever.

VAN CREVELD, Amsterdam, Netherlands.

CLINICAL OBSERVATIONS IN ACUTE RHEUMATISM. III. P. H. KRAMER, Nederl. tijdschr. v. geneesk. **83**:881 (Feb. 25) 1939.

In his third contribution on the subject of rheumatic fever Kramer gives some particulars of the disease in children. Attention is paid to the peculiar localization of the articular lesions, which may give rise to a suspicion of meningitis. Pancarditis is considered, and more particularly recurrent rheumatic chorea and its similarity to the hyperkinetic form of epidemic encephalitis. Lastly "abdominal rheumatism" of the infantile period is discussed.

VAN CREVELD, Amsterdam, Netherlands.

Chronic Infectious Diseases

THE RESISTANCE OF AVIAN TUBERCLE BACILLI TO LOW TEMPERATURES WITH ESPECIAL REFERENCE TO MULTIPLE CHANGES IN TEMPERATURE. P. KYES and T. S. POTTER, J. Infect. Dis. **64**:123 (March-April) 1939.

Kyes and Potter show that tubercle bacilli may survive the lowest obtained temperature, that of liquid helium and also that of liquid air. They demonstrate the fact that these organisms possess extreme power and the ability to retain their viability in the presence of adversely low temperatures.

TOOMEY, Cleveland.

RELATIONSHIP OF PRIMARY (CHILDHOOD) TUBERCULOSIS AND NONSPECIFIC RESPIRATORY INFECTION. H. HOSEN and J. MILES, South. M. J. **32**:387 (April) 1939.

Hosen and Miles state that a primary tuberculous infection, no matter what the age of the patient at the time, has four future possibilities: 1. It may heal completely, so that the patient loses his cell sensitization to tuberculoprotein. 2. It may become quiescent with increase in specific resistance. 3. It may extend immediately and produce death. 4. It may extend later and produce clinical disease and even death after a state of specific resistance has been established.

They have seen many children with so-called activity of primary foci but have been hesitant to describe them as suffering from the effects of tuberculous toxin for the following reasons: 1. After preventorium treatment for active tuberculous infection, many patients failed to show any improvement in their symptoms. 2. The symptoms of cough, instability of the nervous system, tiredness, restless sleep, anorexia, sweating, leukocytosis, rapid heart, anemia and rise of temperature are often associated with nontuberculous disease of the respiratory system even in children with tuberculous infection. 3. The roentgen evidence of tuberculous infection is similar to the roentgen evidence of chronic bronchitis. Thus it is difficult to say whether the exudative process in the hilus is due to tuberculous infection or to nonspecific infection.

The authors conclude that whenever a tuberculous child shows symptoms of an active process, concomitant sinusitis should be looked for before considering an active primary complex.

SCHLUTZ, Chicago.

ERYTHEMA NODOSUM AND TUBERCULOSIS. R. DEBRÉ, Bull. Soc. franç. de dermat. et syph. **45**:1091 (July) 1938.

Debré states that during the past several years he has observed more than 150 cases of erythema nodosum. Only 50 were used as a basis for the present study. To Debré erythema nodosum is always tuberculous. In half the cases roentgenograms showed shadows diagnostic of a primary pulmonary infection. In about half the cases tubercle bacilli were discovered in the sputum or gastric contents, even without characteristic roentgen evidence in the chest. In 2 cases positive evidence of tuberculosis was obtained by inoculating tissue from the cutaneous nodules into monkeys. Tubercle bacilli were found in the blood in 4 cases. A source of tuberculosis was traced in about half the cases. The seasonal nature of erythema nodosum corresponds to similar seasonal variations in tuberculous pleurisy and meningitis. Debré believes that erythema nodosum is not an allergic manifestation of tuberculosis but an inflammatory lesion depending on the actual presence of tubercle bacilli in the nodules.

LAYMON, Minneapolis. [ARCH. DERMAT. & SYPH.]

TUBERCULOSIS IN SCHOOL CHILDREN. H. SUNDELIUS, Finska läk.-sällsk. handl. **81**:102 (Feb.) 1938.

Sundelius reports that 164 (7.7 per cent) of 2,140 school children gave evidence of the presence of recent or old tuberculous disease; 90 had shown symptoms

before, and 74 during, the school period. Percutaneous tuberculin tests on 1,008 children gave the following incidence of positive reactors: among children 7 to 8 years of age, 29 per cent; 9 to 10 years, 39 per cent, and 12 to 13 years, 50 per cent.

WALLGREN, Göteborg, Sweden.

A TUBERCULIN TEST. A. KRISTENSSON, Hygiea **100**:879 (Nov. 30) 1938.

Comparing a cutaneous tuberculin test made by scarification with a scalpel and the intracutaneous test made by injection of 0.1 to 1 mg. of tuberculin, Kristensson concludes that the former test is more reliable than the latter because this gives sometimes a pseudoreaction in tuberculosis-free persons. The intracutaneous test is read after forty-eight hours.

WALLGREN, Göteborg, Sweden.

NEUROSYPHILITIC CHILD IMPROVED AFTER TREATMENT WITH DIPHTHERIA ANTITOXIN. O. ANDERSEN, Nord. med. tidskr. **15**:711 (April 30) 1938.

A boy of 12, suffering from congenital syphilis, with symptoms and signs suggesting dementia paralytica, contracted diphtheria with high fever (41.5 C. [106.7 F.]). He was treated with 30 cc. of antidiphtheria serum, which produced a severe exanthem. A few months later his mental and neurologic symptoms disappeared. The possibility is discussed that the diphtheria or the injection of serum and the serum sickness exercised a healing influence on the syphilitic process.

WALLGREN, Göteborg, Sweden.

CUTANEOUS TUBERCULIN-EPINEPHRINE TEST. O. G. HANSEN, Nord. med. tidskr. **16**:2027 (Dec. 24) 1938.

A scarification 1 to 2 mm. in length is made. Tuberculin 1.7 times stronger than the international standard tuberculin, with an admixture of 1 drop of a 1 per cent solution of epinephrine, is used. The result is read after forty-eight hours. A reaction of 3 mm. extension is considered positive. In a person with slight sensitivity to tuberculin the tuberculin-epinephrine test is regarded as advantageous because it produces a stronger reaction.

WALLGREN, Göteborg, Sweden.

TUBERCULIN TESTS ON CHILDREN OF VARIOUS AGE CLASSES. S. ROHLIN, Svenska läk.-tidning. **35**:1372 (Aug. 26) 1938.

In Göteborg, Sweden, 3,116 infants and children from newborn to 15 years of age admitted to the Children's Hospital and the Fever Hospital and free from active tuberculous disease were tested with intracutaneous injections of tuberculin in doses up to 1 mg. Positive reactions were observed in 1 per cent of the children who were under 1 year of age, in 10 per cent of those who had reached their fifth year, in 27 per cent of those who had reached their tenth year and in 45 per cent of those who had reached their fifteenth year.

WALLGREN, Göteborg, Sweden.

A CASE OF SECONDARY PULMONARY TUBERCULOSIS ("RUNDHERDEN"). K. HOLMDAHL, Svenska läk.-tidning. **35**:2087 (Dec. 16) 1938.

Holmdahl reports the manifestation of secondary pulmonary tuberculosis in the form of large globoid shadows in the roentgenogram three months after the onset of primary tuberculosis in a girl of 15 years. The secondary tuberculosis eventually resolved.

WALLGREN, Göteborg, Sweden.

TERTIARY PULMONARY TUBERCULOSIS IN A GIRL OF THIRTEEN SUCCESSFULLY TREATED BY THORACOPLASTY. G. VALLENTIN, Svenska läk.-tidning. **35**:2173 (Dec. 30) 1938.

The girl acquired erythema nodosum with primary pulmonary tuberculosis, localized to the left apex, in November 1935. She was treated until June 1937. Six months later she commenced to cough. Physical and roentgenologic signs of pulmonary tuberculosis with cavitations at the site of the old primary complex were demonstrated. The sputum contained tubercle bacilli. Thoracoplasty was performed in March and April 1938. The three apical ribs and great parts of the fourth to seventh ribs were extirpated. Recovery followed; the patient was free from fever and cough, and the sputum showed no tubercle bacilli.

WALLGREN, Göteborg, Sweden.

BOVINE TUBERCULOSIS IN MAN IN THE NETHERLANDS. A. C. RUYS, Nederl. tijdschr. v. geneesk. **83**:1001 (March 4) 1939.

Ruys once more concludes from her researches that in Holland, too, the bovine tubercle bacillus is the cause of tuberculosis in a large percentage of the subjects, especially children, and in the large towns as well as in the country. Only the pulmonary tuberculosis of adults in the large towns is nearly always due to the human type. Adult patients in the country not rarely show the bovine type. A close study of the data shows that almost every form of bovine tuberculosis in childhood is a consequence of an infection along the digestive tract. The data speak in favor of the theory that in the majority of adults pulmonary tuberculosis is a consequence of an exogenous renewal of infection.

VAN CREVELD, Amsterdam, Netherlands.

INFLUENCE OF SPLENECTOMY ON THE COURSE OF THE GUINEA PIG TEST FOR CUTANEOUS TUBERCULOSIS. P. H. J. LAMPE, Nederl. tijdschr. v. geneesk. **83**:1718 (April 15) 1939.

Lampe is led to believe that splenectomy does not reduce the resistance of the guinea pig against experimental tuberculosis derived from cutaneous tuberculosis of human or bovine type in man, the differences between 30 splenectomized animals and 30 controls being only slight. This applies to subcutaneous and intraperitoneal infection and to varied intervals between splenectomy and infection (one to twenty-eight days). The result of the animal test was postitive in 17 of 19 cases of cutaneous tuberculosis. Factors taken into consideration were: a histologic control of the tissue material to be used, tests in duplicate, sufficient length of observation (at least two and a half months), careful postmortem examination and, if possible, a second test in case of a negative result.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Blood, Heart and Blood Vessels and Spleen

FOLLOW-UP STUDY OF SYSTOLIC MURMURS. M. J. SHAPIRO, Am. Heart J. **17**:416 (April) 1939.

One hundred and two patients with nonpathologic systolic murmurs were followed over a period of years. The first examination was made during childhood. About half of the patients were followed into early adult life.

At the conclusion of the study the original diagnosis of nonpathologic murmur was believed to be correct in 98 per cent of the cases. GIBSON, Chicago.

PREMATURE CLOSURE OF THE FORAMEN OVALE. M. C. BENNER, Am. Heart J. **17**:437 (April) 1939.

Two cases are reported in which the foramen ovale was functionally closed at birth. One infant was stillborn; the other died eleven hours after birth. Both were markedly edematous, and the body cavities contained free fluid.

The etiologic factors in the condition and the resulting circulatory changes are discussed.

GIBSON, Chicago.

COARCTATION OF THE AORTA, NONCLINICAL TYPE, ASSOCIATED WITH A CONGENITALLY BICUSPID AORTIC VALVE. P. HALLOCK and R. HEBBEL, Am. Heart J. **17**:444 (April) 1939.

Hallock and Hebbel report a case of moderate coarctation of the aorta in which the usual clinical signs of coarctation were lacking. The diagnosis was made during life by visualization of the constricted isthmus in the left oblique roentgenoscopic position. A congenitally bicuspid aortic valve was an associated anomaly, and this valve was the seat of subacute bacterial endocarditis.

Because of the frequency of associated anomalies and the likelihood of complicating bacterial endocarditis, the recognition of nonclinical coarctation of the aorta is important.

GIBSON, Chicago.

DEVELOPMENT OF THE ELECTROCARDIOGRAM OF THE EMBRYONIC HEART. E. C. HOFF, T. C. KRAMER, D. DUBOIS and B. M. PATTEN, Am. Heart J. **17**:470 (April) 1939.

Electrocardiographic records were made from chick embryos in stages of incubation varying from about thirty-six hours to four days. It was found that by the fourth day of development the electrocardiogram has assumed practically the configuration characterizing that of a fully developed chick.

The authors emphasize the fact that at this stage of development the embryonic heart has neither a nerve supply nor a specialized sinoventricular conduction system.

GIBSON, Chicago.

FUNCTIONAL CLASSIFICATION OF CHILDREN WITH HEART DISEASE. M. M. MALINER and W. F. MATTHEWS, Arch. Pediat. **56**:142 (March) 1939.

A group of 200 children with cardiac lesions and 25 children with noncardiac clinical conditions were submitted to the two step stair test as suggested by Master.

The results tend to show that the method offers a reliable means of classifying children with heart disease into the various functional capacity groups as suggested by the New York Heart Association.

Not only did the test serve in the proper grouping of the children into Class 1, 2A, 2B or 3, but the results in percentages served in gaging more accurately the degree of tolerance to exercise.

The variations in blood pressure and pulse rate following the exercise test tended to show that only systolic blood pressure changes were necessary for the proper evaluation of myocardial efficiency.

The measure of the tolerance for exercise as determined by the two step test is fairly constant, and this serves as an added means of judging myocardial improvement in cases of deficiency.

The exercise tolerance test has shown that clinical interpretation of myocardial efficiency is approximately 20 per cent incorrect, and the authors endorse the two step test as a valuable method for properly ascertaining the functional capacity of children with heart disease.

ORR, Buffalo.

A Case of Pericarditis of Unrecognized Etiology. E. R. Reynolds, Arch. Pediat. **56**:158 (March) 1939.

The author believes the condition of his patient may have been due to a deficiency of vitamin B. Recovery followed vitamin B therapy.

Orr, Buffalo.

Estimation of Albumin and Globulin in Blood Serum II and III. H. W. Robinson, J. W. Price and C. Hogden, J. Biol. Chem. **126**:207 (Nov.) 1938.

Robinson, Price and Hogden describe a method for the determination of albumin and globulin fractions of serum. In a previous communication they described a special method of filtration of the globulin-precipitate. The present method consists in precipitating the globulin with 1.5 molar sodium sulfate and separating the precipitate by means of an angle centrifuge. The results obtained compare favorably with their results by the filtration method. The advantages of centrifugation are that it requires a smaller amount of serum and it is a faster method than filtration. The original determinations were carried out at temperatures of 37 C. In the second communication, the authors made duplicate determinations at 25 C. (the usual room temperature) and 37 C. and found that the higher temperature was not necessary for accuracy.

Limper, Louisville, Ky.

Agranulocytic Syndrome in Children. G. Paisseau, J. Ferroir and J. Gautier, Arch. de méd. d. enf. **42**:137 (March) 1939.

Agranulocytosis in the form described first by Schultz is encountered only exceptionally in early life; atypical forms have been reported in 38 instances. Protocols of 3 further cases are contributed by the authors, together with detailed studies of the blood. The patients were children of 13 months, 3 years and 10 years, respectively. The youngest patient made a good recovery through transfusions and iron therapy; the child of 3 died within a week after admission to the hospital, while the eldest of the series was still under observation.

Amesse, Denver.

Fatal Hemorrhage Due to Lack of Fibrin in Infant's Blood. J. Wolff, Jahrb. f. Kinderh. **148**:33 (Nov.) 1936.

A child of 5 weeks was brought to the clinic with symptoms dating from the fourth week of age. At that time he was observed to have many petechial hemorrhages in the skin, hemorrhages in the scleras, suggilations about both shoulder blades and conjunctival bleeding in addition to icterus.

Following venipuncture, the blood continued to flow from the area of the puncture. The blood taken from the vein remained in a fluid state for hours. The child died before a blood donor could be found.

The platelets were normal; the bleeding time was greatly prolonged, and the fibrin content was considerably lower than normal. Syphilis, hemophilia, scurvy and Werlhof's disease were ruled out.

The icterus mentioned is looked on by the author as a sign of hepatic damage which preceded this marked deficiency of fibrin.

The reports of 2 similar cases in the literature are reviewed. In both these cases the hemorrhage was associated with a deficiency of fibrin. Hepatic disease was not demonstrated in these instances.

Landau, Hannibal, Mo.

Influence of Vitamin B on the Reticulocyte Count in the Blood of the Sick Child. M. Sauer, Jahrb. f. Kinderh. **148**:80 (Nov.) 1936.

Vitamin B was given orally in the form of yeast and parenterally in the form of levurin (a proprietary preparation containing B_1). The response in small children and nurslings was only slightly greater than that in older children.

Tuberculous children and those ill with infections of the respiratory tract showed no noteworthy response to ingested yeast. The results in children with furunculosis were similar in that nothing striking was noted.

Children with Perthes' disease, celiac disease and chorea minor showed a noteworthy response. In children with chorea minor the clinical response, in addition to the rise in reticulocytes, to the vitamin B therapy was most striking. This was also observed in children with Perthes' disease.

A 1½ year old boy who had been unsuccessfully treated with iron and liver for severe familial anemia showed an enormous increase in reticulocytes, up to 284 per cent, which paralleled the increase in erythrocytes and hemoglobin. In no other instance was the result so striking. This speaks well for the combination of liver, vitamin B and iron in treatment of this condition.

LANDAU, Hannibal, Mo.

FOCAL MYOCARDITIS CAUSED BY INFLUENZA. J. KRAMÁR, Orvosi hetil. **82**:599 (June 18) 1938.

Kramár describes the focal myocarditis which may occur even in cases of very light influenza. The myocardial alterations are mostly poor in clinical symptoms; only electrocardiographic examination can demonstrate the myocardial lesions. The electrocardiographic alterations were: deviation of the ST section and negative T wave. The sedimentation rate of the red blood cells was in most cases normal; this can be taken as a symptom differentiating influenza from rheumatism, because in the latter condition the rapidity of sedimentation is generally very decided. These focal myocardial lesions disappeared in every case in some months. The children should lie in the fresh air till the electrocardiogram definitely shows evidence of recovery.

GÖTTCHE, Budapest, Hungary.

ELECTROCARDIOGRAMS TAKEN DURING EFFORT FOR CHILDREN WITH HEART DISEASE. P. KISS, Orvosi hetil. **82**:802 (Aug. 13) 1938.

Kiss first made an electrocardiographic examination of the child at rest; then the child sat up and bent from the waist and straightened till it grew tired, and again an electrocardiographic examination was made. These examinations were made in 129 cases. Only children with heart trouble were examined. The cardiac difficulty was of various degrees. Kiss could not find any data by which one could reckon the work ability of the heart.

GÖTTCHE, Budapest, Hungary.

SENSITIVENESS OF HEART MUSCLES TO CERTAIN INFECTIONS. I. ÉDERER and I. ZÁRDAY, Orvosi hetil. **82**:822 (Aug. 20) 1938.

Ederer and Zárday made extensive examinations (clinical, roentgenographic and electrocardiographic) of 91 children who suffered from influenza, tonsillitis or rheumatism. The clinical and roentgenologic examinations did not show any pathologic changes in most cases, but the electrocardiographic alterations were mostly very plain. Low voltage was found in 2 cases, sinoauricular block in 1 case, extrasystoles in 13 cases and pathologic alteration of the T wave in 14 cases. The alterations of the ST section pointed also to focal myocardial lesions. Two thirds of these alterations showed steady improvement in the course of systematic examinations, and they disappeared in two to seventeen months. Not one turned into a chronic organic lesion, so that the aforementioned alterations can be regarded as reversible.

GÖTTCHE, Budapest, Hungary.

THREE KILOGRAM SPLENIC CYST TAKEN FROM A GIRL AGED 11 YEARS. E. KUBÁNYI, Orvosi hetil. **82**:948 (Sept. 24) 1938.

A splenic cyst weighing 3,050 Gm. was taken from a girl aged 11 years. Histologic examination showed that the spleen was completely atrophic. Hematologic examinations before and after the operation did not show any alterations

in the blood picture and in the reticuloendothelial system. It is possible that the pressure of the cyst caused the spleen to atrophy slowly, so that its function gradually ceased even before the operation. GÖTTCHE, Budapest, Hungary.

Diseases of Nose, Throat and Ear

SERUM THERAPY OF STREPTOCOCCIC INFECTION OF THE NOSE, THROAT AND EAR AND ITS COMPLICATIONS. A. E. SHEPLAR, M. J. SPENCE and W. J. MACNEAL, Arch. Surg. **38**:206 (Feb.) 1939.

Additional reports are given on 30 patients suffering from severe infection with hemolytic streptococci in the field of otolaryngology, 4 with complicating meningitis and 15 with blood yielding bacteria on culture. These patients were treated with streptococcus serum of three different kinds. In some instances other therapeutic procedures were used along with the injection of serum. There were 7 deaths in this group. The authors conclude that the early use of chemotherapeutic and biologic agents for the control of infections with hemolytic streptococci may be expected to reduce appreciably the need for operative procedures.

KAISER, Rochester, N. Y.

INCIDENCE OF HEMOLYTIC STREPTOCOCCI IN THE TONSILS OF CHILDREN AS RELATED TO THE VITAMIN C CONTENT OF TONSILS AND BLOOD. A. D. KAISER and B. SLAVIN, J. Pediat. **13**:322 (Sept.) 1938.

This study was undertaken to determine whether in children there is any relationship between the level of the vitamin C stored in the blood and the presence of hemolytic streptococci in the tonsils. A group of 123 children undergoing tonsillectomy were studied. The blood was examined for vitamin C, and the tonsils after removal were cultured for hemolytic streptococci and their vitamin C content determined. The virulence of the streptococci when present was determined by intraperitoneal injections into mice. A higher incidence of streptococci was found in the tonsils of children in whose blood vitamin C was low. The incidence of hemolytic streptococci in freshly removed tonsils was found to be definitely higher for those patients whose blood and tonsils showed low levels of vitamin C, and it was low for children whose blood and tonsils registered higher values for vitamin C. Though the evidence suggests that an adequate amount of vitamin C in the blood influences the incidence of hemolytic streptococci in the tonsils, it is possible that infection of the tonsils causes lowering of vitamin C.

RAUH, Cincinnati.

ACUTE UPPER RESPIRATORY INFECTIONS WITH GASTROINTESTINAL SYMPTOMS. E. D. ANDERSON, Minnesota Med. **21**:611 (Sept.) 1938.

This article calls attention to the frequency with which gastrointestinal symptoms occur in children with respiratory infections. The author emphasizes the importance of examining all children with abdominal pain or vomiting for both respiratory infections and surgical conditions and describes the symptoms, physical findings and treatment of the condition.

ANDERSON, Minneapolis.

TREATMENT OF THE COMMON COLD IN INFANTS AND CHILDREN. R. L. J. KENNEDY, Minnesota Med. **22**:1 (Jan.) 1939.

Under the term "common cold" Kennedy includes acute inflammation of any or all portions of the upper part of the respiratory tract. He feels that the cause may

be a filtrable virus, with bacteria as coincidental or secondary invaders. He advises isolation of infants from infected persons. Treatment may be preventive or symptomatic. Vaccine may be given with the understanding that, although not harmful, it may not prove beneficial. Kennedy feels that proof is lacking that there is any substance in food or in preparations of vitamins which specifically prevents colds. For treatment he advises rest in bed, sedatives, humidity, baths, antipyretics and occasionally the use of epinephrine or ephedrine as nasal drops or a spray.

ANDERSON, Minneapolis.

ALLEGED PAINFUL SEQUELAE AND POOR RESULTS OF ANTROSTOMY. A. B. K. WATKINS, M. J. Australia **1**:302 (Feb. 25) 1939.

Watkins discusses the reasons for the bad repute into which antrostomy has fallen in the minds of both physicians and lay people under the following headings: (1) operations performed in unsuitable cases, (2) unsuitable operations, (3) other nasal lesions which have been overlooked and (4) technical failures in operation.

GONCE, Madison, Wis.

ORIGIN AND CHARACTERISTICS OF LABIAL AND NASAL ANOMALIES IN PERSONS WITH CONGENITAL CLEFTS. F. BURIAN, Časop. lék. česk. **76**:101 (Jan. 29); 138 (Feb. 5) 1937.

Burian discusses the history, fundamentals, pathogenicity, embryogenesis and plastic anatomy of cleft palate and harelip with the idea of improving esthetically the surgical treatment of these anomalies. The irregular dentition is discussed in detail, and the Brophy controversy about the question of cleft of maldeveloped or cleft of normally developed segments is emphasized. The embryology of the head, face and nose is taken up in detail and illustrated with sketches. Photographs of patients before and after operation are shown. STULIK, Chicago.

ASPIRATION OF BLOOD DURING TONSILLECTOMY UNDER LOCAL ANESTHESIA. T. LEEGAARD, Norsk mag. f. lægevidensk. **99**:485 (May) 1938.

During tonsillectomy performed under local anesthesia induced by painting the mucous membrane with pontocaine a large amount of blood and pharyngeal secretion flows down into the lower part of the respiratory tract. If the operation is performed with the patient in the recumbent position, this flowing down of blood and secretion is prevented to a certain degree. Of 1,007 tonsillectomies performed in this way, only 2 were followed by bronchopneumonia, and the bronchopneumonia was mild. Atelectasis was not demonstrable.

WALLGREN, Göteborg, Sweden.

PETROSITIS. P. C. GERLINGS, Nederl. tijdschr. v. geneesk. **83**:504 (Feb. 4) 1939.

By the name "petrositis" Gerlings indicates an inflammation of the cells of the petrous pyramid, the petrosal portion of the temporal bone. He describes the normal and the pathologic types of pneumatization of this area. He calls attention to the studies of Lange and Marx, which show the importance of petrositis in otogenous intracranial involvement. For the diagnosis roentgen examination is indispensable. With regard to the treatment of petrositis the various operations on the petrosal apex are pointed out. The clinical record of a boy of 8 years with petrositis is communicated, with a report of the microscopic examination of the temporal bone.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Lungs, Pleura and Mediastinum

CHILDHOOD PNEUMONIA (COMPLICATIONS AND MORTALITY). C. J. LESLIE, New York State J. Med. **38**:1454 (Nov. 15) 1938.

A study of 511 consecutive cases of pneumonia observed in the Babies' Ward of the New York Post-Graduate Medical School and Hospital is reported. The series included cases of lobar and cases of bronchial pneumonia. The mortality rate was 25 per cent. Empyema occurred in 52 cases. Various factors in pneumonia are discussed.

AIKMAN, Rochester, N. Y.

SPONTANEOUS PNEUMOTHORAX. K. M. A. PERRY, Quart. J. Med. **8**:1 (Jan.) 1939.

Perry studied the causes of spontaneous pneumothorax in a group of 114 patients, treated at the London Hospital in the years 1924 to 1937. In 16 of the patients the condition complicated pulmonary tuberculosis; in 13 it arose from other pulmonary diseases and wounds of the thoracic wall, whereas in 85 (70 per cent) it occurred in a previously healthy subject with no apparent cause.

Perry concludes that the immediate cause of spontaneous pneumothorax is probably always a rupture of an air-containing vesicle into the pleural cavity.

BRADFORD, Rochester, N. Y.

NONTUBERCULOUS PERSISTENT EXTENSIVE PULMONARY DENSITY WITH HEMOPTYSES DUE TO BRONCHIAL STENOSIS IN A YOUTH FOURTEEN YEARS OLD. P. ARMAND-DELILLE and INBONA, Bull. Soc. pédiat. de Paris **36**:586 (Oct.) 1938.

A boy 14 years old had repeated hemoptysis. A tuberculin test was positive. A tentative diagnosis of pulmonary tuberculosis was made, but repeated attempts to demonstrate tubercle bacilli in the sputum failed. After instillation of iodized poppyseed oil 40 per cent and use of the bronchoscope it became evident that there was stenosis of the left bronchus with suppuration of the left lung.

BENJAMIN, Montreal.

TEN MONTHS OF LATENCY OF A CHRONIC RESIDUAL PULMONARY ABSCESS IN AN INFANT TWENTY MONTHS OLD. CAYLA, DELON and CORCELLE, Bull. Soc. pédiat. de Paris **36**:597 (Oct.) 1938.

A boy had a pulmonary abscess at the age of 4 months. After a period of five months he was considered well. When he was 20 months old, bilateral bronchopneumonia developed, and he died. Necropsy revealed a chronic encysted abscess in the lower lobe of the right lung at the cardiohepatic angle. He had had no fever and raised no sputum and had recovered from measles without any complication in the interval.

BENJAMIN, Montreal.

EPIDEMIC OF SUBACUTE INFECTIOUS PULMONARY EDEMA IN INFANTS (FROTHY BRONCHOALVEOLITIS). P. LEREBOULLET, M. LELONG, J. DELARUE and JOSEPH, Bull. Soc. pédiat. de Paris **36**:621 (Oct.) 1938.

An epidemic of acute infection of the respiratory tract occurred in an infants' ward. The symptoms were severe paroxysmal coughing, aggravated when the patient was disturbed, as by a change of position, feeding or other activity, and whitish frothing at the mouth. Showers of fine moist rales were scattered throughout the lungs. Most of the infants recovered after five to ten days, although in

some the condition lasted up to twenty-seven days. Eight infants, most of them premature, died out of a total of 28. Necropsy in the few cases in which it was performed showed bronchopneumonia.

BENJAMIN, Montreal.

PULMONARY ABSCESS IN CHILDREN WITH PARTICULAR REFERENCE TO THE POSSIBILITY OF RECOVERY. R. POHL, Jahrb. f. Kinderh. **148**:38 (Nov.) 1936.

Pulmonary abscess occurs much more frequently in children than is generally believed. There is a tendency toward multiple abscesses, especially in infants.

Several case reports are given, illustrating the tendency to respond to conservative measures. This tendency is much more pronounced in children than in adults. In many cases the average period of illness is four to five weeks. Pohl advises a delay of six to eight weeks (provided no alarming symptoms supervene) before resorting to a major surgical operation.

LANDAU, Hannibal, Mo.

CONGENITAL CYSTIC LUNG. J. FRIMANN-DAHL, Norsk mag. f. lægevidensk. **99**: 181 (Feb.) 1938.

A newborn boy suffered from congenital cystic involvement of the right lung. Cyanosis and dyspnea were noted at birth. A roentgenogram made on the second day of life showed displacement of the heart to the left side and multiple air blebs in the right lung field. The infant died three weeks later, and the postmortem examination confirmed the clinical diagnosis: There was a large air-filled trabecular cyst in the lower lobe of the right lung.

WALLGREN, Göteborg, Sweden.

INTRACRANIAL COMPLICATIONS IN EIGHT CASES OF ACUTE PNEUMONIA AND WHOOPING COUGH. P. SELANDER, Svenska läk.-tidning. **35**:861 (June 10) 1938.

1. A boy of 19 months who was suffering from rather fresh primary tuberculosis acquired whooping cough. During the first week of this superimposed illness he presented symptoms and signs of meningitis (226 cells per cubic centimeter of spinal fluid, 86 per cent of which were mononuclears; no tubercle bacilli). There was slow regression, with recovery. He was healthy for two years; then he died from tuberculous meningitis. At necropsy no changes were demonstrable that could be ascribed to the first attack of meningitis. This complication was regarded as due to the whooping cough.

2. A girl of 2 years who was suffering from whooping cough showed in the sixth week of illness signs of intracranial disease. The cerebral lesion eventually was found to be a tumor (meningioma of the choroid plexus of the left lateral ventricle). She died shortly after operation.

3. Localized encephalitis producing ocular symptoms and flaccid paresis occurred in a 2 year old girl suffering from acute pneumonia. She was discharged healthy.

4. Hemiplegia was observed in a boy of 5 years during convalescence from lobar pneumonia. Recovery took place with rest.

5. Cerebral hemorrhage was produced by a thrombous in the sinus cavernosus in a rachitic girl 1 year of age, on the tenth day of acute bronchopneumonia.

6 and 7. A boy of 15 and a girl of 6 years displayed symptoms of acute (toxic?) encephalitis with coma in the beginning of acute lobar pneumonia localized at the base of the lung in the first patient and at the hilus in the second. The cerebral symptoms disappeared gradually after the crisis.

8. A boy of 6 years with central pneumonia showed papilledema, rigidity of the neck, slight pathologic changes in the spinal fluid, uneasiness and involuntary movements. He recovered from the nervous symptoms and signs after the crisis.

WALLGREN, Göteborg, Sweden.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

SPREADING PERITONITIS COMPLICATING ACUTE PERFORATIVE APPENDICITIS. J. O. BOWER, J. C. BURNS and H. A. MENGLE, Arch. Surg. **37**:751 (Nov.) 1938.

It is brought out in this study that approximately 300,000 persons in the United States are operated on annually for acute appendicitis and its complications and that 20,000 of these die at an average age of 27 years. Fewer than 2,000 die of acute appendicitis, while more than 17,000 die of peritonitis. In cases in which the appendix is unruptured less than 1 per cent die. In cases in which peritonitis is present the mortality ranges from 18 to 33 per cent.

Realizing that the use of laxatives plays a part in the spreading of peritonitis, the authors conducted experiments on dogs to determine the effect on the mortality of various forms of treatment for laxative-induced spreading peritonitis. The dogs were treated by various routes with horse serum, Bacillus perfringens (Clostridium welchii) antitoxin, blood transfusions, immune blood serum and lyophilized immune serum. There was a marked difference in the mortality in the various groups, ranging from 91 to 25 per cent. The minimum mortality was noted in the group treated with B. perfringens antitoxin.

KAISER, Rochester, N. Y.

SUBPHRENIC ABSCESS IN CHILDREN WITH SPECIAL REFERENCE TO ROENTGEN SIGNS OF TRANSPHRENIC INFECTION. W. E. ANSPACH, J. Pediat. **13**:157 (Aug.) 1938.

Ten cases of subphrenic abscess in children are reported in detail, and illustrations from 3 additional cases are included. Roentgenograms are an important adjunct to the history and clinical findings and seldom fail to offer important evidence of this disease, often enabling one to make the diagnosis. Fixation of the diaphragm is the earliest roentgenographic sign, evidence of diaphragmatic pleurisy next, then signs of a small accumulation of fluid which tends to remain small in amount, and later, even in cases in which treatment has been neglected and there is extensive empyema, evidence of an almost normal contact of the visceral and diaphragmatic pleurae (in overexposed films). The roentgen signs which are almost pathognomonic of this disease are the shadows of "gas and fluid level" beneath the right leaf of the diaphragm. The latter signs were present in only one fourth of the cases presented. Roentgen signs of pneumonitis and collapse of the lower lobe of the lung are occasionally associated findings as the infection invades or surrounds the lung tissue. A local basal pneumothorax is prone to follow a bronchial fistula, with or without spontaneous healing. A rest cavity is more common than in primary pulmonary disease. In the majority of cases the abscess follows appendicitis. Small perforations in other viscera are thought to account for it in most cases in which it is on the left side. The latter shows a greater tendency to heal spontaneously than the right-sided lesion. Waiting for definite roentgen signs of a loculation before establishing drainage seems to be judicious.

RAUH, Cincinnati.

PNEUMATOSIS OF THE INTESTINE IN INFANCY. T. W. BOTSFORD and C. KRAKOWER, J. Pediat. **13**:185 (Aug.) 1938.

Pneumatosis of the intestine is rare. Only 5 cases of the condition in childhood and infancy have been recorded prior to this report. Botsford and Krakower present abstracts of the records on 6 cases, 5 of which were observed during a period of approximately one year. Emphysema of the intestinal wall is thought to result from penetration of gas from the intestinal lumen. The gas enters the wall through minute or microscopic defects in the mucosa; it may form local cysts or it may permeate the wall and form cystic aggregates at points distant from the site of entrance. Increased intragastric or intraintestinal pressure is probably of impor-

tance in initiating, and peristaltic activity in determining the site of, the emphysema. Enteritis may be an important factor in the genesis of this condition. In 5 of the 6 cases reported there occurred persistent vomiting and diarrhea or diarrhea alone. There were glandular changes and inflammatory reactions in the small intestines, but no gross ulceration. These findings were present in the emphysematous regions and in distant areas. With these changes, especially with hyperemia and hyposecretion of mucus, minute fissures in a relatively dry and friable mucous membrane could allow continued entrance of gas. Disturbances in peristalsis and intraintestinal gaseous pressures could coexist with enteritis. An increase or a disturbance in lymphatic drainage, such as is evidenced by the fairly frequent observation of dilated lymphatics in the intestinal wall and dilated active sinusoids in the mesenteric lymph nodes, would facilitate the diffusion or accumulation of gas. It is well known that gas permeates lymphatic channels. The mesenteric lymph nodes were the seat of gas cysts in 3 of the reported cases, and in 1 the cisterna chyli and thoracic duct were also involved. RAUH, Cincinnati.

IMMEDIATE OR DEFERRED SURGERY FOR GENERAL PERITONITIS ASSOCIATED WITH APPENDICITIS IN CHILDREN. W. E. LADD, New England J. Med. **219**:329 (Sept. 8) 1938.

This very practical paper by an experienced surgeon should be read by every pediatrician (and surgeon). It contains too much "meat" for a short abstract.

The author's methods are best evaluated by his results. His conclusions are as follows:

"Too many children die from the complications of appendicitis.

"The obvious solution to this situation is early diagnosis and early operation, which limits the problem to one of acute appendicitis without complications. In this stage of the disease the mortality is negligible.

"The unwise use of cathartics in the presence of abdominal pain is an important factor in causing peritonitis to result from appendicitis and in keeping up a high mortality.

"Delayed operation or the Ochsner treatment is probably less effective in the child than in the adult but is occasionally desirable, even in the child. Its employment should be limited to surgeons of experience. When incorrectly used and misapplied, it is harmful, not helpful." GENGENBACH, Denver.

PYLORIC STENOSIS CURED BY OPERATION; INTOLERANCE TO COW'S MILK; DISSOCIATION OF THE TWO SYNDROMES. LESNÉ, CAYLA and CORTEEL, Bull. Soc. pédiat. de Paris **36**:413 (June) 1938.

A 21 day old boy with pyloric stenosis was operated on by the Fredet method. He continued to vomit and had digestive disturbances due to intolerance for cow's milk. Human milk in gradually diminished amounts and skimmed decaseinated cow's milk were used with beneficial results. BENJAMIN, Montreal, Canada.

CONGENITAL STENOSIS OF THE RECTUM WITH PROBABLE MEGARECTOSIGMOID. M. LELONG, J. RACHET, P. AIMÉ and GARNIER, Bull. Soc. pédiat. de Paris **36**:418 (June) 1938.

A 6 month old infant had stricture of the rectum 3 cm. above the anus. The infant had frequent small stools, which were evacuated by straining. At the age of 5 months the appetite diminished and the weight began to drop. There was a large fecal impaction. Roentgen examination showed the rectal ampulla and sigmoid to be large and distended. Repeated dilatation was begun, and it was thought that eventually surgical intervention would be required.

BENJAMIN, Montreal, Canada.

TREATMENT OF MEGACOLON BY SYMPATHECTOMY. J. CALVET, Progrès méd., Oct. 22, 1938, p. 1427.

In this discussion of sympathectomy in the treatment of megacolon Calvet points out that a careful study of each patient should be made before this type of operation is undertaken. A patient in whom a mechanical obstruction can be shown to be present is, of course, unsuitable. Also in the patient in whom the musculature of the colon has degenerated until the colon has become similar to a fibrous sack no improvement can be expected from operation. As a preoperative test for the muscular efficiency of the colon, Calvet advises observation of the patient under a fluoroscope after the giving of a barium sulfate enema and the production of lumbar anesthesia. A patient suitable for operation shows marked peristalsis and rapid evacuation of the colon. Various operative technics are discussed.

LESLIE, Evanston, Ill.

MILIARY TUBERCULOSIS IN THE PANCREAS OF CHILDREN. H. W. SACHS, Frankfurt. Ztschr. f. Path. **51**:63, 1938.

Prompted by Ghon, Sachs examined 20 cases of generalized miliary tuberculosis in order to see if there were changes in the pancreas. The histologic examination by serial sections showed that in 70 to 84 per cent of the cases miliary tubercles were present in the pancreas. Most of the tubercles were found in the peripheral portions of the pancreas and in the head of the pancreas.

SAPHIR. [ARCH. PATH.]

ORIGIN OF SUMMER DIARRHEA IN INFANCY. H. SCHONFELD, Med. Klin. **34**:1154 (Sept. 2) 1938.

Overfeeding and hot weather may predispose to diarrhea by causing stasis of intestinal contents and migration of bacteria from the lower to the upper portion of the intestinal tract. However, the exogenous factor (bacterial contamination of food) is most important. Symptoms of intoxication may precede diarrhea. Bacillus coli is the most common contaminating organism.

SIEMSEN, Chicago.

OCCURRENCE OF ENTEROBIUS VERMICULARIS IN APPENDIXES REMOVED SURGICALLY AND THOSE STUDIED POST MORTEM. O. FÜSTHY, Ztschr. f. Kinderh. **60**:394 (Dec. 19) 1938.

Pinworms were found in 20 per cent of 500 appendixes removed surgically and in 6 per cent of 300 studied post mortem. In only 2 surgical specimens was pinworm infestation the only pathologic observation and thus the apparent cause of the clinical picture of appendicitis. Invasion of the appendical wall by pinworms seemed secondary to damage of the tissue by invading organisms or other agents. A postmortem study of different parts of the intestine revealed that the appendix was never infested alone, and the author considers removal of the appendix as a part of the cure for pinworms fallacious. He calls attention to the high incidence of pinworm infestation in Hungary and to the importance of its eradication.

SIEMSEN, Chicago.

INTERMITTENT JUVENILE JAUNDICE. E. MEULENGRACHT, Hospitalstid. (supp.) **81**: 117 (Sept. 19) 1938.

Twenty-four cases of very slight, benign, chronic, intermittent jaundice in young persons are reported. The jaundice presented itself clinically as a slight yellowish tinge of the scleras and sometimes of the skin. The icteric index of the blood serum varied from 7 to 25. The urine was pale, occasionally containing

urobilin; in other respects it was normal. The stools were of normal color. The only symptom of the more icteric periods was fatigue. The jaundice persisted for decades; the intensity was of varying degree and was accentuated by intercurrent diseases, such as gastrointestinal disorders, common colds, overwork and lack of sleep. The spleen and liver were not enlarged. The fragility of the erythrocytes was normal. No microcytosis, no increase of the reticulocytes, no anemia was noted. This frequent familial disease is regarded as due to a certain congenital inferiority of the functional capacity of the liver.

WALLGREN, Göteborg, Sweden.

ACUTE APPENDICITIS IN SMALL CHILDREN. P. BULL, Norsk mag. f. lægevidensk. **99**:1065 (Oct.) 1938.

Bull reports 52 cases of appendicitis in children under 6 years of age (31 boys; 21 girls). Five of the children were only 20 to 23 months old. Fourteen children suffered from diffuse peritonitis (4 deaths), 3 from multiple abscesses (2 deaths) and 21 from single abscesses (2 deaths). Forty-three of the patients had gangrenous appendicitis and in 23 the process perforated. Fecal concretions were found in 22 cases. The death rate was 15.4 per cent (the average for children is 5.9 per cent). Of 18 children operated on within forty-eight hours, none died; of 21 children operated on the third to fourth day, 6 died; of 7 children operated on the fifth to sixth day, 1 died, and of 6 children operated on in the second week, 1 died. The following features of appendicitis in small children are emphasized: 1. Even in infants who suddenly become ill with vomiting, abdominal pain and fever appendicitis should be suspected. 2. Appendicitis at this age is often combined with diarrhea and disorders of micturition. 3. The higher death rate is due to greater diagnostic difficulties. 4. Sometimes the diagnosis must depend solely on information given by relatives.

WALLGREN, Göteborg, Sweden.

CLINICALLY ATYPICAL ACUTE EPIDEMIC HEPATITIS. P. SELANDER, Svenska läk.-tidning. **35**:2006 (Dec. 2) 1938.

This is a description of acute hepatitis (catarrhal jaundice) as observed in 5 patients. The first, a girl of 4, had an enlargement of the liver so great that the border was felt at the umbilicus. In the second, a girl of 12, the acute hepatitis did not heal. There were several relapses, with eventual signs of chronic hepatitis. The third, a girl of 5, died from the hepatitis on the seventh day. At the postmortem examination the liver was enlarged; histologically it showed round cell infiltration and liver cell degeneration and enlargement of the lymph nodes at the porta hepatis. The fourth patient, a girl of 3, had had one attack of epidemic hepatitis seven months previously with recovery. In the fifth, a boy of 9, diabetes mellitus became manifest during the convalescent period after the hepatitis.

WALLGREN, Göteborg, Sweden.

GLYCEROPHOSPHATASE IN FECES. L. KOSTER, Nederl. tijdschr. v. geneesk. **82**:5856 (Dec. 10) 1938.

The presence of a glycerophosphatase in human feces is reported with a method for determining its amount. The ferment is activated by the magnesium ion from the food. In nontropical sprue fecal phosphatase, determined after this method, is diminished or absent. Drugs likewise can influence the level. In leukemia high values are found; a hypothesis is given on the connection with leukopoiesis.

VAN CREVELD, Amsterdam, Netherlands.

Nervous Diseases

MENINGITIS CAUSED BY ATYPICAL GRAM-NEGATIVE COCCI. H. A. REIMANN and R. W. KOUCKY, J. Bact. **37**:409 (April) 1939.

Reimann and Koucky studied 2 patients with meningitis which was associated with atypical bacteria. From the first patient a gram-negative diplococcus with characteristics different from other classified strains was isolated. It gave rise to two interchangeable colony forms. From the second patient, two species of cocci were obtained; one was a type I meningococcus, which had the unusual ability to grow on plain agar at room temperature and had gram-positive elements, while the other was a staphylococcus, which was represented by three interchangeable colony forms.

These studies suggest that under ordinary routine laboratory examination atypical colonies may appear on culture plates. Such colonies are usually ignored or dismissed as contaminants but actually may be part of the pattern of variation of the bacterium concerned. Recognition of the phenomenon of bacterial variation and type transformation would remove much confusion and would probably reduce the number of separate varieties of bacteria now believed to exist.

STOESSER, Minneapolis.

AGENESIS OF THE CORPUS CALLOSUM. J. S. LLOYD, J. Ment. Sc. **84**:995 (Nov.) 1938.

Over 100 cases of agenesis of the corpus callosum are on record. Lloyd reports the case of an idiot girl who died of pneumococcic meningitis at the age of 9 years. She was microcephalic, the cranial circumference being 17 inches (43 cm.). She had spastic quadriplegia and bilateral atrophy of the optic nerve, with absence of the light reflex. Several degenerative phenomena were in evidence, including facial asymmetry, strabismus, scoliosis and attacks of grand mal. Post mortem a large fibroma was seen in the wall of the left ventricle of the heart, which almost obliterated the cavity but had given rise to no murmurs or other cardiac signs during life. The brain presented pneumococcic meningitis. The cerebral hemispheres were small, weighing only 8½ ounces (240 Gm.) each. Microgyria was absent. On separating the hemispheres, complete absence of the corpus callosum was revealed. No clue was obtained as to the cause of the condition. The family history was unsatisfactory.

KASANIN, Chicago. [ARCH. NEUROL. & PSYCHIAT.]

OCCURRENCE OF THE RARER DEMYELINATING DISEASES (NEUROMYELITIS OPTICA, SCHILDER'S ENCEPHALITIS ET CETERA) IN SOUTH AUSTRALIA. E. W. HURST, C. T. C. DE CRESPIGNY and H. K. FRY, M. J. Australia **1**:451 (March 25) 1939.

Three cases of the diseases named in the title are described.

GONCE, Madison, Wis.

FACIAL NAEVUS FLAMMEUS, CEREBRAL ANGIOMA AND GLAUCOMA. D. MANOLESCO, D. LAZARESCO and D. VINTILESCO, Rev. d'oto-neuro-opht. **16**:664 (Dec.) 1938.

The classic, symptomatic triad of Schirmer-Sturge-Weber's disease — naevus flammeus, glaucoma and cerebral symptoms with intracranial calcifications — is extremely rare. Only 68 cases have been reported, in all of which nevus and glaucoma were associated, and in some of them cerebral angioma was surely or probably present. The facial nevus may be bilateral; it is usually unilateral and is on the same side as the glaucoma. Bilateral glaucoma is exceptional. The location of the intracranial angioma varies, resulting in a multiplicity of neurologic symptoms: epilepsy, hemianopia, the adiposogenital syndrome, imbecility and psychic

disturbances. The authors report a typical case in which the nevus involved both sides of the face, the mucosa of the mouth and palate and the right eyelid, conjunctiva and choroid. An absolute glaucoma without buphthalmia, associated with deep excavation of the disk and blindness, was present in the right eye. The nervous manifestations were epilepsy in infancy, a mental depressive state, cerebellovestibular disturbances (nystagmus, pendular reflexes, deviation to the left) homonymous hemianopia. A roentgenogram showed a calcified vessel in the right occipital region. Fourteen cases in which histologic examination was made of the enucleated eyeball were discovered in the literature. In only 3 of these was there no intraocular vascular disease. Only when there has been complete anatomic examination of serial sections of the entire choroid may it be determined that there are no angiomatous changes present. If all patients with naevus flammeus of the face were subjected to a complete ophthalmologic and neurologic examination, the glaucoma might be arrested or retarded in its development and the associated intracranial angioma submitted to treatment.

DENNIS, San Diego, Calif. [ARCH. NEUROL. & PSYCHIAT.]

LITTLE'S DISEASE AND EPILEPSY. M. BIRO, Schweiz. Arch. f. Neurol. u. Psychiat. **42**:1, 1938.

Biro selected from a group of 35 cases in which there were various types of cerebral diplegia, paraplegia and hemiplegia of childhood 10 in which convulsive seizures had been recorded. In 3 cases the cerebral palsy became manifest at the end of the first year, during the course of which the children had had one or two convulsions. Seizures preceded the appearance of signs of cerebral involvement by a few months in the fourth case and continued to recur with the progress of the disease. The interval between the onset of convulsions and that of the paralysis was only a few days in 2 cases, but whereas in one of these the attacks ceased to recur, in the other the patient later became subject to localized tonic spasms. In another case one convulsion occurred at the onset of the cerebral palsy and another a year later. Convulsions preceded other symptoms by a few months in 3 cases and recurred later, but in only 1 case did they continue to recur in the later course of the disease.

Biro expresses the view that convulsions in Little's disease generally appear in the early stages. In most cases, including those in which there is a series of attacks, the seizures cease sooner or later, although prognosis is difficult in this respect even after prolonged observation. In addition to the anatomic changes, certain physiologic factors, chemical or physical, probably play a part in the genesis of the convulsions. There is no correlation between the type of cerebral palsy and the frequency of epileptic attacks, nor are mental disturbances more frequent in patients who have convulsions than in those who do not. Control of the seizures is always important; in cases in which the evidence of cerebral damage is slight it is the main task.

DANIELS, Denver. [ARCH. NEUROL. & PSYCHIAT.]

FAMILIAL RUDIMENTARY MULTIPLE SCLEROSIS AND HEREDITARY ANOMALIES OF THE ABDOMINAL REFLEXES. HEINZ WILLACH, Ztschr. f. d. ges. Neurol. u. Psychiat. **164**:392 (Jan.) 1939.

Willach reports on two families with multiple sclerosis. The first family consisted of 5 siblings, 2 of whom had a definite mild form of multiple sclerosis of long standing; the other 3 members showed significant diminution of the abdominal reflexes. Tremor of the hand and temporal pallor were noted in persons who did not have definite multiple sclerosis. The second family presented a less definite picture. Two brothers had no abdominal reflexes, and in 2 others these reflexes were easily exhaustible or not elicitable in one quadrant. Three maternal uncles and aunts, the father and his 2 sisters had abnormal abdominal reflexes.

The abdominal reflexes were studied in the relatives of 105 patients with disseminated sclerosis, in 101 relatives of tabetic patients and in the relatives of 200 persons used as controls. They were found to be abnormal in 11.9 per cent of the multiple sclerosis group, in 1.7 per cent of the control group and in 2.1 per cent of the tabetic families. These abnormalities of the abdominal reflexes occur with significantly greater frequency in the relatives of patients with multiple sclerosis. The difference in the frequency of such anomalous reflexes in the multiple sclerosis and in the control group is more than three times the probable error. These observations are much in favor of the theory that genetic factors are of etiologic importance in multiple sclerosis.

SAVITSKY, New York. [ARCH. NEUROL. & PSYCHIAT.]

DIAGNOSTIC VALUE OF WELTMANN'S COAGULATION BAND IN THE SPINAL FLUID OF INFANTS WITH MENINGITIS. F. MORI, Acta pædiat. japon. **45**:360 (March) 1939.

The Weltmann reaction was carried out by adding 0.5 cc. of the spinal fluid to 5.0 cc. of calcium chloride solutions, representing concentrations of the salt of 1.0, 0.9, 0.8, 0.7, 0.6, 0.4, 0.3, 0.2 and 0.1 per cent, in 10 test tubes, which were then immersed for fifteen minutes in boiling water. Normal cerebrospinal fluid produces no coagulation, but pathologic specimens give varying degrees of coagulation. The coagulation band, however, bears no direct relation to either the cell count or the globulin content of the fluid. During the terminal stage of tuberculous meningitis there is a tendency for the coagulation band to diminish.

KATO, Chicago.

TUBEROUS SCLEROSIS OF THE BRAIN, WITH VAN DER HOEVE'S RETINAL PHACOMAS. M. ANKER and A. KVEIM, Acta ophth. **16**:454, 1938.

Tuberous sclerosis of the brain manifests itself by the formation of multiple tumor-like foci in the central nervous system, retina, skin, kidneys, heart, thyroid and mammary glands and sometimes in the skeleton. The disease is hereditary and appears in childhood, the patients showing late development and retarded mentality. Death before the age of 30 is usual.

Sclerotic foci are found in the cortex, in the central ganglions and in the walls of the lateral ventricles. These consist of a rich glial proliferation with large peculiar cells, which are in part atypical ganglion cells and in part atypical glial cells. The ventricular tumors are often calcified. The cutaneous changes are called "adenoma sebaceum" and are found especially on the sides of the nose, on the cheeks and on the chin, but they may occur anywhere on the surface of the body. The fundi show typical tumor formations and occasionally atrophy of the optic nerve. The disease is closely related to Recklinghausen's and to Lindau's disease.

In all 3 of the cases reported by the author there were observed: thin connective tissue veiling the papilla; strands along the retinal vessels; raspberry-like white tumors; small, flat, slightly protruding white foci; small areas of choroidal atrophy. These observations correspond to those of van der Hoeve, published in 1921. The histologic structure of the retinal tumors has been described by van der Hoeve. Such tumors arise from the nerve fiber layer and to a less extent from the ganglion cell and inner plexiform layers. They consist of nerve fibers and glial tissue and also contain large undifferentiated cells, which are held to be forerunners of glial and ganglion cells. Usually these tumors remain unchanged for years and do not damage the eye except to reduce visual acuity if they are situated on the papilla.

O. P. PERKINS. [ARCH. OPHTH.]

EXOPHTHALMOS COINCIDENT WITH INTRACRANIAL TUMORS. H. SKYDSGAARD, Acta ophth. **16**:474, 1938.

The author limits his remarks to tumors arising from the cerebrum, meninges and cerebral vessels. Exophthalmos was found in 14 of a series of 352 patients with such tumors, seen at the Rigshospital. The exophthalmos was unilateral in 9.

The tumors are tabulated as follows:

Meningioma of the pterygoid bone	5	(unilateral 4) (bilateral 1)
Parasagittal meningioma	1	(bilateral)
Convexity meningioma	1	(unilateral)
Meningioma of the olfactory nerve	1	(bilateral)
Neurinoma of the acoustic nerve	1	(unilateral)
Tumor of the hypophysis	3	(unilateral)
Aneurysm of the carotid artery	1	(bilateral)
Glioma of the temporal lobe	1	(bilateral)

Similar sets of figures from the published series of other authors are given.

The author remarks that while papilledema and exophthalmos may occur together, they by no means necessarily do so; nor does exophthalmos seem to have any definite relation to increased intracranial pressure.

O. P. PERKINS. [ARCH. OPHTH.]

SULFANILAMIDE IN INFLUENZAL MENINGITIS. T. HALBERTSMA, Maandschr. v. kindergeneesk. **8**:273 (April) 1939.

A girl of 3½ years with meningitis caused by the bacillus of influenza recovered when treated with large doses of sulfanilamide combined with vitamin D. The author is skeptical, however, in regard to this therapy, as spontaneous recoveries from this kind of meningitis also occur—especially since the recovery took a long time, whereas the drug used has a quick effect, and since in ordinary influenza sulfanilamide is usually without a favorable effect; also, of the patients with influenzal meningitis treated with sulfanilamide whose cases are described in the literature, none have recovered.

VAN CREVELD, Amsterdam, Netherlands.

BORIUM AS AN ANTIEPILEPTIC REMEDY. A. VERJAAL, Nederl. tijdschr. v. geneesk. **83**:1227 (March 18) 1939.

One hundred epileptic adults who had several seizures or the equivalents weekly in spite of their regular use of large doses of phenobarbital were treated with a combination of this drug and boric preparations. In 13 patients the seizures were stopped; in 27 their number was reduced to less than one third. The toxic symptoms observed and their possible causes are discussed; stress is laid on the risk of intoxication. The results of an investigation of boric metabolism which are communicated led to the assumption that the favorable effect of borium can be ascribed to an influence of this element on the biologic state of the organism.

VAN CREVELD, Amsterdam, Netherlands.

Psychology and Psychiatry

THE INCIDENCE AND CHARACTER OF MASTURBATION THREATS IN A GROUP OF PROBLEM CHILDREN. MABEL HUSCHKA, Psychoanalyt. Quart. **7**:338 (July) 1938.

The histories of a group of 320 problem children were studied to determine how many of them had been threatened or punished for masturbation. It was found that 128, or 40 per cent, had been threatened drastically. Physical threats were used most commonly; over half the children had been threatened with genital injury. The threat usually emanated from the mother or mother substitute.

This study is of special interest because it presents a body of factual material which indicates that at present children who masturbate are often threatened with castration. This fact has important implications with respect to castration anxiety.

PEARSON, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

MENTAL DEFICIENCY IN CHILDHOOD. N. HOBHOUSE, Practitioner **142**:481 (April) 1939.

Mental deficiency in children is not easily recognized by parents, and it usually falls to the physician to diagnose or to suspect it in the first instance. It is important that he should do so when the child is under his observation rather than that the defect should be detected by others after unsuitable educational experiments have been made. On the other hand, it is a diagnosis which should not be communicated to parents unless it is beyond doubt, for on this the physician can never afford to be wrong. The difficulties inherent in making the diagnosis will be greatly diminished if it is considered in two independent steps. The first of these is to recognize mental retardation; the second is to decide whether the retardation is due to a true mental defect or whether it is occasioned by some physical ailment or unfavorable environmental condition.

Severe grades of amentia—idiocy and imbecility—become manifest in infancy and early childhood, whereas high grade feeblemindedness may pass unrecognized until puberty or early adolescence. The diagnosis of such a condition will usually be achieved on the appearance of the infant, on the behavior in early childhood and on the educability during the school period, confirmed by the application of intelligence tests.

From a purely clinical point of view, mentally deficient children fall into two main classes: simple primary aments, and special types in whom the defect accompanies congenital or developmental disorders. The latter will usually be recognized by some feature in their appearance; the former have no special physical characteristics and the diagnosis is arrived at by inference, their subnormality not being attributable to any other cause.

GELSTON, San Francisco.

NERVOUS CHILDREN AND MODERN TREATMENT. R. MILLER, Practitioner **142**:488 (April) 1939.

In a pleasing Brennemannian manner this article suggests that the study and treatment of nervous children on purely psychologic lines may be overdone and that such a narrow outlook is not without its drawbacks. Four possible sources of danger are discussed: (1) overlooking ill health and fatigue as causes determining the onset and character of nervous symptoms; (2) attributing to psychotherapy improvement which is due to natural development; (3) producing in parents overanxiety for their children's psychologic health, and (4) inculcating bizarre and harmful methods in education. Such dangers are enhanced at a time like the present, when interest in matters psychologic is so widespread among the laity.

Further, it is suggested that there are signs of reaction against at least some of the tenets of modern psychology and that not a few parents would enjoy their children more if they could bring them up in a less "medicated" atmosphere. More particularly, they wish to feel free to discipline their children by teaching them such things as they have found to be of value in their own lives, so that the young minds may be trained to form judgments rather than merely exhibit "reactions."

GELSTON, San Francisco.

CATALEPSY IN YOUNG CHILDREN. P. H. FIEDELDY DOP, Nederl. tijdschr. v. geneesk. **83**:164 (Jan. 14) 1939.

A girl of 3½ years for three months showed unmistakable catalepsy; this gradually disappeared during the following months. Then she had severe rickets.

He thinks that there may be an indirect relation between the two conditions. Rickets forms a great obstacle to the development of the will and mentality. The author tries to demonstrate that this retardation may be the cause of the catalepsy.

VAN CREVELD, Amsterdam, Netherlands.

TREATMENT OF SO-CALLED INFANTILE NEUROSES. H. C. RÜMKE, Nederl. tijdschr. v. geneesk. **83**:483 (Feb. 4) 1939.

Rümke designates the following points in the treatment of infantile neuroses as the most important: One should keep in mind that these "neuroses" can vary a great deal as to genesis. According to their genesis, they can be divided into the following groups: constitutional nervousness, "emotional–hyperesthetic weakness" conditions, functional disturbances, true infantile neuroses, psychopathies, developmental disturbances and disturbances of puberty. The last mentioned can be divided into disturbances of individualization and of regulation and integration of the desires and aspirations active in puberty. Treatment must be directed to the causative factor if possible. The available methods of treatment are given, and the indications for their application are considered separately for the above-mentioned groups.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Genitourinary Tract

UNDESCENDED TESTES. W. O. THOMPSON and N. J. HECKEL, J. A. M. A. **112**:397 (Feb. 4) 1939.

Thompson and Heckel evaluate the present status of glandular therapy for undescended testicles. They find their results to be less favorable than those of others, having 20 to 30 per cent success, compared with 60 per cent in the literature. The important factor in statistics is a proper evaluation of the cases as to the presence of pseudocryptorchidism or of mechanical obstruction to descent. Surgical repair is aided by treatment, owing to the enlargement of the structures, but treatment should be stopped before genital hypertrophy becomes excessive.

HEERSMA, Kalamazoo, Mich.

TUMORS OF THE KIDNEY IN CHILDREN. H. P. KERR, J. A. M. A. **112**:408 (Feb. 4) 1939.

Adenosarcoma is the most frequent tumor of the kidney and is usually found in children under 6 years of age. It is highly malignant, only 2 of Kerr's 14 patients living over four years after admission to the hospital. His recommended treatment is preoperative irradiation until the tumor no longer regresses and then removal. Metastases and recurrences also are irradiated.

HEERSMA, Kalamazoo, Mich.

INFECTION OF THE IMMATURE VAGINA. G. C. SCHAUFFLER, R. KANZLER and C. SCHAUFFLER, J. A. M. A. **112**:411 (Feb. 4) 1939.

The authors evaluated the various methods of treatment of gonorrheal infection in the immature vagina from the study of 256 cases of their own and 261 cases in which sulfanilamide was used by others. Their conclusions are that an estrogen (amniotin) administered vaginally gives a higher percentage of cures (78 per cent) than sulfanilamide given orally (43 per cent). Distention with silver nitrate ointment gave 83 per cent of cures but was cumbersome and lengthy.

HEERSMA, Kalamazoo, Mich.

AETIOLOGY OF CHRONIC NEPHRITIS IN CHILDHOOD. H. J. SINN, M. J. Australia **1**:572 (April 15) 1939.

Sinn reviews the literature on chronic nephritis in childhood. He offers an etiologic classification and suggests that the pathologic and clinical end results in cases of this disease may be due to (1) congenital abnormalities of the urinary system, (2) the terminal stage of acute or subacute nephritis and (3) renal destruction in malignant hypertension. He concludes that there is no connection between congenital syphilis and chronic nephritis. Studies of cases illustrating the various etiologic factors are presented.

GONCE, Madison, Wis.

GENITO-URINARY DISEASE. T. T. HIGGINS, Practitioner **142**:437 (April) 1939.

This article is simply a textbook review of the more common ailments of the genitourinary system.

GELSTON, San Francisco.

NEPHROTIC-GLYCOSURIC DWARFISM WITH HYPOPHOSPHATEMIC RICKETS IN EARLY INFANCY. G. FANCONI, Jahrb. f. Kinderh. **147**:299 (Oct.) 1936.

A series of cases gleaned from his own experience and from the literature was studied. These cases presented the following symptom complex: early appearing dwarfism; rickets; thermolability; albuminuria; glycosuria; glycolability similar to true diabetes without nocturnal hyperglycemia and without acetonuria; pronounced hypophosphatemia with normal or only slightly elevated azotemia.

The most important pathologic change was a fatty vacuolar degeneration of the tubular epithelium of the kidneys as in nephrosis.

LANDAU, Hannibal, Mo.

MEDICINAL AND DIETETIC TREATMENT OF INFECTIONS OF THE URINARY TRACT. J. G. G. BORST, Nederl. tijdschr. v. geneesk. **83**:1739 (April 15) 1939.

Borst reviews the treatment of infections of the urinary tract with a ketogenic diet, with mandelic acid and with sulfanilamide, as well as the indications, the risks and the technics of these three new methods and their advantages over the methods formerly in use. He emphasizes the necessity of using freshly voided urine or catheterized urine in judging of the presence or the absence of urinary infection, the subjective symptoms of the patients being of little use for the diagnosis of chronic urinary infection.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Ductless Glands; Endocrinology

EFFECT OF THYROXINE ON THE ERUPTION OF TEETH IN NEWBORN RATS. D. DARNOFSKY and E. P. CRONKITE, Proc. Soc. Exper. Biol. & Med. **40**:568 (April) 1939.

In newly born rats receiving injections of 100 micrograms of crystalline thyroxine daily for six days the incisor teeth were found to have erupted within seventy to eighty hours after birth, whereas in control animals the incisors were not erupted until between one hundred and twenty and one hundred and thirty hours after birth.

HANSEN, Minneapolis.

THE THYROID GLAND OF THE CRETIN AT BIRTH. J. EUGSTER, Beitr. z. path. Anat. u. z. allg. Path. **100**:392, 1938.

Prompted by the almost complete lack of knowledge of the anatomic state of the thyroid gland of the cretin at birth, Eugster investigated 4 such glands. The findings were not uniform. Two showed a pronounced diffuse parenchymatous

struma, and a third, distinct atrophy and sclerosis. In the fourth there was a slight, probably goitrous enlargement. The difficulty of establishing a clinical diagnosis of cretinism at birth is discussed in the light of the pathologic changes.

R. J. LEBOWICH. [ARCH. PATH.]

THERAPY OF ADDISON'S DISEASE WITH SODIUM CHLORIDE. L. KAGAN and B. HOLCBERG, Jahrb. f. Kinderh. **149**:101 (Nov.) 1936.

Addison's disease is described in a boy of 11 years, a rare occurrence. This boy was brought into the hospital practically moribund but responded to administration of sodium chloride up to 9 Gm. daily while in the hospital. A relapse occurred when he was out of the hospital and was not following instructions, but on reentry he was again successfully treated. Since then he has done well on 6 Gm. daily, in milk.

The authors insert an optimistic note, stating that there is hope that the injection of an extract of the hypophysis containing a specific factor will lead to regeneration of the cortex of the adrenal and to a more lasting cure.

The uncertainty of the efficacy of an extract of the cortex of the adrenal gland, as well as the high cost, was cited as a reason for not using this extract.

LANDAU, Hannibal, Mo.

A STUDY OF THE PANCREAS, HYPOPHYSIS AND THYROID IN CHILDREN OF DIABETIC MOTHERS. H. OKKELS and S. BRANDSTRUP, Acta path. et microbiol. Scandinav. **15**:268, 1938.

The pancreatic islets in children of diabetic mothers are larger and more numerous than is normal. Accompanying the insular hypertrophy there is an increase in the differentiated epithelium of the anterior lobe of the pituitary. The thyroid gland also shows increased activity. All these alterations have a common cause, probably the hyperglycemic condition induced in the fetus. This condition possibly effects the changes observed in the endocrine glands by the intermedium of the central nervous system. FROM AUTHORS' SUMMARY. [ARCH. PATH.]

A CASE OF THE LAURENCE-MOON-BIEDL SYNDROME. G. VON BAHR and A. NORDMARK, Hygiea **100**:928 (Dec. 15) 1938.

The patient was a boy of 10 years. The mother was mentally deficient and had 4 children of 3 fathers. The boy was born at full term. The first symptoms were ocular. Difficulties appeared at 1 year of age and increasing adiposity at 2 years of age; imbecility was demonstrated at the age of 4. Genital hypoplasia and retinal degeneration, but no polydactylia, were found. WALLGREN, Göteborg, Sweden.

TUMOR OF THE HYPHOPHYSIS IN A CHILD. A. BRODIN, Nord. med. tidskr. **15**:585 (April 15) 1938.

A girl of 10 years with symptoms of diabetes insipidus was first seen one year previous to the time of report. Roentgenologically the sella turcica was normal, and the visual fields were normal at that time. A year later there was a defect of the sella with manifest bitemporal hemianopia. Radiologic treatment gave some amelioration of the defect of vision; the polyuria remained unchanged.

WALLGREN, Göteborg, Sweden.

PROGNOSIS OF MYXEDEMA. L. FAÇEE SCHAEFFER, Maandschr. v. kindergeneesk. **8**:244 (March) 1939.

The prognosis of myxedema depends on the therapy. Excessive doses of thyroid preparations are not so dangerous as doses which are too small; frequent controls and confinement in the hospital are recommended in order that the optimal doses may be administered. VAN CREVELD, Amsterdam, Netherlands.

DEATH BY HYPOGLYCEMIA DURING TREATMENT WITH PROTAMINE ZINC INSULIN. J. GROEN and A. H. GARRER, Nederl. tijdschr. v. geneesk. **83**:1844 (April 22) 1939.

Groen and Garrer describe fatal hypoglycemia observed in a pregnant diabetic woman who received 52 units of protamine zinc insulin and 12 units of regular insulin in one injection per day. The patient was in the eighth month of pregnancy, and a cesarean section was made when the heart sounds could no longer be heard. The fetus was dead. This is the eighth case in which protamine zinc insulin has been either the main or a contributory cause of death.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Muscles, Bones, Joints and Lymph Glands

MYOTONIA CONGENITA TREATED SUCCESSFULLY WITH ADRENAL CORTEX (ESCHATIN). M. H. WEINBERG, Ann. Int. Med. **12**:1382 (Feb.) 1939.

A girl aged 20 months, whose symptoms appeared at the age of 16 months, was given an extract of adrenal cortex (eschatin) subcutaneously in doses of 0.5 cc. at the rate of three injections a week for six weeks, two injections a week for six weeks and one to two injections a week for eight weeks. Complete recovery resulted.

READING, Galveston, Texas.

POSTERIOR DISLOCATION OF LOWER FEMORAL EPIPHYSIS IN BREECH DELIVERY. M. S. BURMAN and M. J. LANGSAM, Arch. Surg. **38**:250 (Feb.) 1939.

Posterior dislocation of the lower femoral epiphysis is an injury occurring at birth, conditioned by severe trauma during prolonged delivery by breech presentation in a primipara. Four cases of the injury are reported. This dislocation is the reverse of the usual anterior dislocation of this epiphysis observed in adolescents. The femur was not fractured in any of the living babies. The deformity is a flexion deformity of the knee, with more or less valgus of the knee. This deformity gives rise to a swelling of the knee joint and of the femur adjacent to it. The involved lower extremity is limp, and the passive motions of the affected knee are painful. Roentgenograms aid in the diagnosis. The defect requires simple treatment with use of traction or of a cast to hold the knee extended. The prognosis is excellent for useful function of the injured part.

KAISER, Rochester, N. Y.

BACTERIOLOGY AND IMMUNOLOGY OF CHRONIC STAPHYLOCOCCAL OSTEOMYELITIS: II. THE EFFECT OF THE INFLAMMATORY TISSUE ON ANTIGENS AND ANTIBODIES. K. E. HITE, J. Infect. Dis. **64**:93 (Jan.-Feb.) 1939.

It is commonly observed that the development of chronicity of an osteomyelitic lesion is usually considered evidence of clinical improvement. Hite reports an instance in which he found that pus from sinus tracts chronically inflamed did not destroy staphylococcus toxin, botulinum antitoxin and horse plasma. In fact, enough horse plasma remained in the sinus tract for two days to be detected by biologic anaphylactic reactions.

TOOMEY, Cleveland.

OSTEOSARCOMA OF THE SUPERIOR MAXILLA IN CHILDREN. P. ORSINI, Med. inf. **10**:75 (March) 1939.

A boy of 5 years had a rapidly growing tumor of the upper jaw near the left deciduous molars. Exophthalmos resulted, and there were metastases in the pleura and in the abdomen. The child died fifty days after the first symptoms. No histologic or roentgenologic data are given.

HIGGINS, Boston.

CONGENITAL KYPHOSIS. F. DREHMANN, Beitr. z. klin. Chir. **165**:595, 1937.

Drehmann describes a case of congenital kyphosis due to a "semivertebra" in the dorsal area. He also reports 2 cases of gibbus due to *Block Wirbel* (block whirl).

He describes the difference between congenital kyphosis and acquired kyphosis, especially that due to infection (spondylitis). He also differentiates between the kyphosis due to anomaly of the vertebral column and that seen in patients with chondrodystrophy.

RUBIN, Boston.

MYOTONIC DYSTROPHY. E. KATZENSTEIN, Schweiz. Arch. f. Neurol. u. Psychiat. **42**:249, 1938.

This study was prompted by the finding of myotonic dystrophy with juvenile cataract in 3 siblings and in 3 of their second cousins, who were likewise siblings. A fourth child in the second family had an incipient cataract, but did not have myotonic dystrophy. All the patients were seen at intervals over a period of from four to five years, the presence of lenticular changes being confirmed in each instance by observations with a slit lamp. Information was obtained with regard to 107 members of the family, comprising 7 generations. The majority of the 93 members still living were examined personally. The patients with myotonic dystrophy belonged to the sixth generation; their great-grandfather was born in Württemberg, Germany, in 1818, and the respective paternal grandfathers migrated to Switzerland, where they married.

Five of the patients presented the complete syndrome of myotonic dystrophy, whereas the sixth had only mild myotonia, though presenting generalized dystrophy of high degree. Three of the patients were hindered by the myotonia in earning a livelihood. Muscular atrophy varied somewhat in degree and distribution from one patient to another, the muscles involved being those of facial expression and mastication, the sternocleidomastoid muscles, the small muscles of the hands and feet and the muscles of the forearms and legs. The characteristic thin face and tired expression were pronounced in 5 cases. Atrophy of the musculature of the eyelids was noted in 3 cases, and closure of the lids was weak in another. Atrophy of the soft palate, though rare in myotonic dystrophy, was found in 4 of the cases reported. One patient had difficulty in swallowing. Loss of tendon reflexes was infrequent, but Chvostek's sign was elicited in 5 cases.

Myotonia of the muscles of the hands came on during adolescence or earlier in all of the cases reported. One patient noticed the symptom as early as the eleventh year, and her sister and brother first experienced it in the fifteenth and seventeenth year, respectively. Contrary to general experience, furthermore, each of these 3 patients showed signs of cataract as early as three years after the onset. Routine use of the slit lamp would probably reveal lenticular changes relatively early in many cases of myotonic dystrophy.

The hair of the head was thin or falling out in 3 cases, and in another the beard was sparse. In all 6 cases there was acrocyanosis; in 1 case slight changes in temperature induced vasospastic phenomena, with marked blanching of the fingers. One patient had small testes, and another, a woman with undeveloped breasts, complained of irregular menstruation. Two patients in the second family had been operated on for goiter; another member who did not have myotonic dystrophy suffered from hyperthyroidism. The patient whose myotonia was of slight degree presented an infantile, dysplastic habitus. In contrast to other members of their respective families, the 6 patients all showed defects of intelligence or personality.

The father of the first 3 patients evidently had mild myotonia, but showed no muscular atrophy, although his hands and fingers were small and he had acrocyanosis. His tendon reflexes were unobtainable, and he had had a cataract in one eye which later had been enucleated because of secondary glaucoma. The great-grandfather of all 6 patients and 2 of his daughters had senile cataracts. The view is expressed that the early appearance of cataracts in the patients with myotonic

dystrophy may be an example of anteposition. Contrary to the experience of other observers, the tendency to cataract and myotonic dystrophy was transmitted solely in the male line. Anomalies of the teeth, jaws and palate were frequent, not only in the patients and their immediate relatives but also in collateral lines. The tendency toward diseases of the thyroid gland was attributed to the introduction of this tendency into one branch of the family through marriage rather than to the polyglandular disturbance frequently encountered in myotonic dystrophy. No instance of inbreeding could be discovered.

Katzenstein comments on the sudden appearance of myotonic dystrophy in one generation of the family studied and its tendency to appear at approximately the same period of life in all cases. It is assumed that the disease was the expression of a dominant trait which was nevertheless pleiotrophic and therefore tended to express itself in varoius forms. The author also expresses the view that myotonic dystrophy is not primarily a myopathy or due to an endocrine dysfunction, but that it is the result of changes in the central nervous system, presumably in the vegetative centers. DANIELS, Denver. [ARCH. NEUROL. & PSYCHIAT.]

CALCIUM AND PHOSPHORUS METABOLISM IN OSTEOMALACIA: VII. THE EFFECT OF ULTRAVIOLET IRRADIATION FROM MERCURY VAPOR QUARTZ LAMP AND SUNLIGHT. H. I. CHU, T. F. YU, K. P. CHANG and W. T. LIU, Chinese M. J. **55**:93 (Feb.) 1939.

This communication comes from the department of medicine of the Peiping Union Medical College. Four Chinese women with osteomalacia and a 13 year old boy with tetany were treated, 3 with artificial radiation and 2 with sunlight. Charts and tables are furnished to illustrate the effects on metabolism and on clinical symptoms. The ultraviolet ray produced results identical with those from the administration of vitamin D, and heliotherapy in early summer in Peiping exerted a helpful antirachitic effect similar to that of exposure to the artificial ultraviolet ray. NEFF, Kansas City, Mo.

TWO CASES OF MYOSITIS OSSIFICANS. T. FRÖLICH, Norsk mag. f. lægevidensk. **99**:440 (April) 1938.

The first patient was a boy of 3, first seen at the age of 2. Shortly after his birth the mother had observed that his left leg could not be extended at the hip joint. At the age of 4 months roentgen examination disclosed a tumor-like involvement of the left hip. When he was 2 years of age this "tumor" was found to be ossified and was regarded as a congenital malformation. The "tumor" was extirpated with a good functional result. Six months later he was seen again. He then suffered from acute myositis of the muscles of the neck, and six months later the same symptoms became localized to the back. Biopsy showed hyperplasia of myxofibrous connective tissue with atrophy of the muscles.

The second patient was a girl. The parents and their other children were healthy. The first symptoms of myositis ossificans were noted when the patient reached the age of 1½ years. The changes were localized to the neck. Gradually the disease spread downward, and when the child was 8 years of age it involved a great part of the muscles of the upper half of the back and the neck. The head and the scapula were fixed. The corresponding muscles were transformed into masses hard as bone. The same changes to a less degree were seen in some parts of the muscles of the breast. Both children were given a ketogenic diet and ammonium chloride. WALLGREN, Göteborg, Sweden.

A CASE OF BESNIER-BOECK DISEASE. A. VON WESTRIENEN, Maandschr. v. kindergeneesk. **8**:262 (April) 1939.

A girl of 13 years presented Besnier-Boeck disease. There was swelling of all superficial groups of lymph nodes, and there were numerous subcutaneous small tumors, also knotty parotid glands and slight deviations in the cornea and in

the capsule of the lens. A roentgenogram of the lungs showed the typical pseudomiliary picture, with severe enlargement of the lymph glands. The phalanges showed small deviations. Biopsy of a lymph node and of a subcutaneous tumor, which appeared to be situated in the muscular tissue, confirmed the diagnosis. The therapy consisted in administration of arsenic and rest in bed. The tumors and the lesions in the lungs soon disappeared. Tuberculin tests were negative, as they generally are in analogous cases. VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Eye

MYOPIA DURING SCHOOL YEARS. E. JAEGER, Klin. Monatsbl. f. Augenh. **101**: 205 (Aug.) 1938.

Jaeger refracted the eyes of 350 girls, aged from 10 to 16, and of 150 boys, aged from 10 to 18 years, between 1926 and 1935. The patients were inmates of two boarding schools and were reexamined at intervals for several years. It was the author's purpose to study the percentage of myopia, its increase and the possible influence exerted by the mode of living and the surrounding conditions. Myopia of more than 0.75 diopter was fully corrected, and glasses of from this strength to 1.5 diopters were worn only during the lessons; those of a high degree, however, were worn constantly. Myopia of over 5.0 diopters was not encountered. Jaeger found that myopia begins at the average age of 12 years and appears never to develop after the fifteenth year of life. The progress of myopia, on the other hand, had not stopped at 18 years in some cases. The largest percentage of progressive myopia was noted at the ages of 11 and 12 years. There was a correlation between age and bodily development and onset of myopia, but no connection with the mental requirements of those pupils could be discovered. K. L. STOLL. [ARCH. OPHTH.]

DACRYOCYSTITIS IN CHILDREN, WITH PARTICULAR REFERENCE TO NEGLECTED CONGENITAL STENOSIS OF THE NASOLACRIMAL DUCT. K. O. GRANDSTRÖM, Acta ophth. **16**:512, 1938.

Of 28 cases of dacryocystitis in children from 1 to 15 years of age, the cause in 9 was probably neglected congenital stenosis of the nasolacrimal duct.

O. P. PERKINS. [ARCH. OPHTH.]

INHERITANCE OF TOTAL COLOR BLINDNESS. J. SANDERS, Nederl. tijdschr. v. geneesk. **83**:1939 (April 29) 1939.

By an inquiry among oculists in Netherlands total color blindness was found in 20 members of 16 families. This anomaly is transmitted by monorecessive heredity. VAN CREVELD, Amsterdam, Netherlands.

Skin Diseases; Allergy

HEREDITARY TRANSMISSION OF LYMPHOGRANULOMATOSIS VENEREA. W. E. COUTTS and O. MONETTA H., J. Trop. Med. **41**:279 (Sept. 1) 1938.

In 1936 Dick cited a case of unusual interest, that of an infant 2 weeks of age with a positive Frei test. Both the father and the mother were known to have lymphogranuloma venereum. Dick was of the opinion that intrauterine infection had occurred.

The authors cite one of their own cases in which a mother who had a severe form of the disease (positive Frei test) delivered an infant whose Frei test on the second and third days of life was negative. Examination of the placenta showed no lymphogranulomatous lesions.

The authors feel that the question of the hereditary transmission of lymphogranuloma venereum should be studied further and that the scanty data at hand permit no definite conclusions.

LAYMON, Minneapolis. [ARCH. DERMAT. & SYPH.]

COMMENT CONCERNING QUESTION OF ERYTHEMA NODOSUM. L. M. PAUTRIER, Bull. Soc. franç. de dermat. et syph. **45**:1046 (July) 1938.

Pautrier states that he discussed the subject of erythema nodosum at great length with Debré, who defended the theory of internists and pediatricians, that tuberculosis is the predominant and perhaps the sole etiologic factor, while Pautrier held to the view of most dermatologists, that erythema nodosum is a symptom complex due to multiple causes. Pautrier explained the differences in opinion in the following way: Erythema nodosum in infants, usually seen by pediatricians, has a tuberculous background in almost all, whereas the disease in adults, studied most frequently by dermatologists, may be an accompaniment of diverse infections, such as syphilis, lepra and trichophytosis.

Pautrier believes that erythema nodosum and erythema multiforme in all probability have the same genesis, that they may represent cutaneous sensitization to the same etiologic agents in different planes. He mentions the occurrence of erythema multiforme in 5 of 26 cases of erythema nodosum.

LAYMON, Minneapolis. [ARCH. DERMAT. & SYPH.]

ERYTHEMA NODOSUM IN INFANT. E. LESNÉ, Bull. Soc. franç. de dermat. et syph. **45**:1086 (July) 1938.

From 1920 to 1938 Lesné observed 96 cases of erythema nodosum, a condition which in an infant he regards as a definite sign of a primary tuberculous infection, equaling in importance the tuberculin reaction or phlyctenular conjunctivitis. In 50 per cent of the cases it was possible to find a source of tuberculosis within the family. In 95 of the 96 cases the tuberculin reaction became positive during the course of the eruption. LAYMON, Minneapolis. [ARCH. DERMAT. & SYPH.]

ETIOPATHOGENIC STUDY OF THIRTY-EIGHT CASES OF ERYTHEMA NODOSUM. E. RAMEL, Bull. Soc. franç. de dermat. et syph. **45**:1138 (July) 1938.

In a long article Ramel expresses his views concerning erythema nodosum. His conclusions are as follows:

1. So-called idiopathic erythema nodosum is always a cutaneous manifestation of tuberculous bacillemia, in adults as well as infants. There is usually a primary infection, although in adults there may be a superinfection. From a biologic point of view erythema nodosum is a tuberculid—i. e., an allergic manifestation produced by the hematogenous propagation of tubercle bacilli of modified virulence.

2. Symptomatic or secondary erythema nodosum is to be divided into two classes: (*a*) one clinically no different from the idiopathic type, with a tuberculous background and brought about by a biotropic mechanism like that occurring in syphilis or following childbirth; (*b*) one of toxi-infectious origin, homologous with true erythema nodosum but distinguishable by its etiologic agents (various bacteria, toxins and fungi). The terms "erythema nodosum" and "dermatitis contusiformis" should be reserved for only the first type, while eruptions of the other type should be designated as "id" eruptions, nodose trichophytids and the like).

LAYMON, Minneapolis. [ARCH. DERMAT. & SYPH.]

ERYTHEMA NODOSUM AND POLYMORPHOUS ERYTHEMA. H. GOUGEROT, Bull. Soc. franç. de dermat. et syph. **45**:1195 (July) 1938.

After a long discussion Gougerot concludes that polymorphous erythema in its various types (purpuric, erythematous, papular, nodular, nodose) is a syndrome

related to different bacteria (most frequently tubercle bacilli) acting on a sensitized terrain. This view explains the identity of the reactions to various causes, the evolution and the good prognosis, since polymorphous erythema represents a victorious defense reaction. LAYMON, Minneapolis. [ARCH. DERMAT. & SYPH.]

A CASE OF ANNULAR GRANULOMA. J. HALLÉ, Bull. Soc. pédiat. de Paris **36**: 388 (June) 1938.

A boy 3 years old was presented showing cutaneous lesions of both legs, which were called "granulome annulaire," a condition which resembles tuberculid and sarcoid, according to some observers. The tuberculin reaction was negative.

BENJAMIN, MONTREAL, CANADA.

KELOID OF THE LOBULE OF THE EAR WHICH RELAPSED THREE TIMES AND WHICH WAS CURED BY ASSOCIATION OF EARLY RADIOTHERAPY WITH SURGERY. FÈVRE, THIBONNEAU and CAYLA, Bull. Soc. pédiat. de Paris **36**: 404 (June) 1938.

A girl 11 years old had prominent keloids on the lobules of the ears. This condition occurred following piercing for earrings. These growths were excised three times but recurred each time. Excision was again performed on the right ear and on the neck, where a keloid was also present, and radiotherapy was begun twelve days postoperatively and used intensively. The result obtained was much better than on previous attempts. BENJAMIN, Montreal, Canada.

FROM ECZEMA TO ASTHMA. P. WORINGER, Bull. Soc. pédiat. de Paris **36**:406 (June) 1938.

One third of a group of asthmatic children had previously had eczema. In 15 to 20 per cent of children who have eczema asthma develops, in a large number before the age of 5 years. Food plays an important role in producing asthma in patients who give a history of eczema, and frequently a digestive disturbance accompanies the respiratory difficulty. In children with asthma who have not had eczema inhalants are more apt to have a causal significance. The roles of infection and climatic conditions are discussed, and it is concluded that when these factors are etiologic the attacks are more catarrhal than spasmodic.

BENJAMIN, Montreal, Canada.

OSLER'S TELANGIECTASIA HAEMORRHAGICA HEREDITARIA. ALBIN PROPPE, Dermat. Wchnschr. **106**:233 (Feb. 26) 1938.

Proppe was able to trace through three generations the family tree of a couple both of whom had Osler's disease. In the second generation 4 of 9 members gave evidence of this disorder, and in the third, 3 of 13. Three suicides occurred.

TAUSSIG, San Francisco. [ARCH. DERMAT. & SYPH.]

INHERITANCE OF ECZEMA, ESPECIALLY NEURODERMATITIS. H. HRUSZEK, Dermat. Wchnschr. **106**:239 (Feb. 26) 1938.

Hruszek reports a case in which the mother and 2 children of a patient with neurodermatitis had the same condition. A second patient with neurodermatitis had 2 children similarly affected. The author believes that this disorder is apt to be inherited. TAUSSIG, San Francisco. [ARCH. DERMAT. & SYPH.]

PATHOANATOMIC CHANGES IN THE CENTRAL NERVOUS SYSTEM IN INFANTILE ACRODYNIA. J. RUESCH, Schweiz. Arch. f. Neurol. u. Psychiat. **42**:361, 1938.

Studies of the pathoanatomic picture and genesis of acrodynia have in general been inadequate. Ruesch reports the case of a boy aged 22 months who lost

his appetite and began to vomit frequently three months before admission to the hospital. After an attack of acute cystitis a month later, he became irritable and apathetic. A rubeoliform rash appeared on the trunk, and the hands and feet became reddened, cold and cyanotic. Pyoderma with crusting, which was noted on the occasion of the first examination, became aggravated; subcutaneous abscesses developed, and the child died a week after admission.

Gross examination of the central nervous system revealed nothing abnormal. Though various stains and impregnation methods were employed, no significant alterations of the ganglion cells could be demonstrated. Throughout the brain and spinal cord blood vessels with dilated adventitial lymph spaces, surrounded by clusters of glia cells, were occasionally seen. Though the cells were mainly of the oligodendroglia variety, a few were of the plump, or *gemästete,* cell type. There was considerable persistence of the subependymal germinal layer, and in the immediate neighborhood of the entire ventricular system were seen germinal centers containing oligodendroglia and macroglia cells, in addition to less mature forms. Precapillaries surrounded by an increased number of oligodendroglia cells were seen throughout the same area; they were most numerous, however, in the corpus callosum and anterior commissure. Indications of receding myelination gliosis were also noted. No changes were noted in the lateral horns of the spinal cord or in the sympathetic ganglions.

The view is expressed that the changes seen in the blood vessels are not specific for acrodynia but are attributable to the infection which complicated the disease in its later course. Significance is attached, however, to the persistence of the subependymal germinal layer and the germinal centers, both of which usually disappear before the eighth month of life. It is suggested that the retarded development of the brain may have rendered it more susceptible to the action of certain endogenous or exogenous noxae. With reference to the increased number of perivascular oligodendroglia cells, the view is expressed that immature perivascular cells may react to noxious agents in this manner. The common occurrence of acrodynia in the second and third year of life is emphasized.

DANIELS, Denver. [ARCH. NEUROL. & PSYCHIAT.]

IDIOSYNCRASY FOR COW'S MILK. G. VON SYDOW, Nord. med. tidskr. **15**:585 (April 15) 1938.

In the 4 cases reported the idiosyncrasy was manifest even at the first ingestion of cow's milk. Two of the infants had symptoms only from the digestive tract and were desensitized (spontaneously?) in a few months. The third and fourth infants suffered from atopic eczema; they were seized with asthma as soon as they received cow's milk. They could not be desensitized; one of them, now 8 years old still has symptoms of sensitivity to cow's milk.

WALLGREN, Göteborg, Sweden.

A CASE OF PROGRESSIVE LIPODYSTROPHY. Å. BRODIN, Svenska läk.-tidning. **35**:2088 (Dec. 16) 1938.

A girl of 12 presented the typical picture of progressive lipodystrophy, the first symptom of which was observed three years previously.

WALLGREN, Göteborg, Sweden.

A SEVERE CASE OF ACRODYNIA. G. BOSSCHER, Maandschr. v. kindergeneesk. **8**:286 (April) 1939.

Bosscher describes acrodynia in a girl of 4 years. She had severe trophic lesions of the skin and mucous membranes and a pyoderma caused by Staphylococcus pyogenes aureus. Contrary to all expectation, she recovered following a laborious therapy, including blood transfusion and treatment with an autogenous vaccine.

VAN CREVELD, Amsterdam, Netherlands.

FAVUS AND SCHOOL. H. W. SIEMENS and A. J. M. KRENS, Nederl. tijdschr. v. geneesk. **82**:6224 (Dec. 31) 1938.

In order to combat favus, the doctors and public and school authorities must be enlightened so that close cooperation may be possible. Children suffering from favus should come to school wearing a closely fitting head bandage, and they should be submitted to regular medical control. Older persons who have this disease should not be allowed to work in environments where they may infect others; in this respect there should be police regulations.

VAN CREVELD, Amsterdam, Netherlands.

ACRODYNIA WITH GANGRENE OF HANDS AND FEET. C. H. VERBOOM, Nederl. tijdschr. v. geneesk. **83**:1362 (March 25) 1939.

After a review of the complications occasionally found in acrodynia (shedding of teeth, intussusception, pneumonia, gangrene of the nose and limbs), Verboom records a case. A girl aged 3 years showed, at the onset of the disease, an extensive scaly and itching exanthem on the trunk. Subsequently there supervened shedding of the teeth, necrosis of the oral mucous membrane and extensive gangrene of the hands and feet. The child died seven weeks after the onset of the disease.

VAN CREVELD, Amsterdam, Netherlands.

Surgery and Orthopedics

USE OF VINYL ETHER (VINETHENE) IN INFANCY AND CHILDHOOD (REPORT OF 100 CASES). R. E. GROSS, New England J. Med. **220**:334 (Feb. 23) 1939.

The type of case in which vinyl ether anesthesia is particularly useful is often encountered in the work of outpatient departments or in the pediatrician's practice.

Vinyl ether (vinethene) was employed as a general anesthetic for a series of 100 infants and children ranging from 1 month to 11 years of age. It was found extremely satisfactory for minor operative procedures, and in no case was there any alarming or untoward reaction accompanying or following the use of it. The extremely rapid induction of anesthesia by this drug permitted full muscular relaxation in thirty or forty-five seconds. The period of recovery was likewise short, and in practically all cases the patient had regained consciousness in two or three minutes; the older children were talking and sitting up by the end of this time. There was postanesthetic vomiting in only 5 cases. The drug can be given easily and quickly on an open mask, and when thus employed in the present series it was always satisfactory.

Vinyl ether appears to be the safest and most satisfactory general anesthetic yet produced for operative procedures of five or ten minutes' duration in infancy or childhood. The cost of the anesthetic is moderate, ranging from 25 to 40 cents in the average case.

GENGENBACH, Denver.

POSTURAL DEFECTS IN ELEMENTARY SCHOOL CHILDREN. G. A. CALDWELL, New Orleans M. & S. J. **91**:601 (May) 1939.

Posture is more than a matter of personal appearance, more than poise, grace and balance; it represents the sum of inherited physical characteristics plus the effect of the habits acquired since infancy.

To ascertain to what extent postural defects were present in children, a survey was made of a private school with 103 children divided among the first nine grades. The survey revealed that the majority of children on entering school and throughout the elementary school years were either underweight or overweight as a result of maintenance on unbalanced diets. Most children in the first five years of school had inadequate chest expansion.

Postural deviations of the head, shoulders, trunk and spine were present in 50 to 60 per cent of the children. Deformities or weakness of the knees and ankles appeared in 80 to 90 per cent of the younger children and in 50 to 70 per cent of the older ones. Most of the shoes and socks worn were poorly fitted. Seating arrangements and desks contributed to poor posture.

The correction of these faults demands a program of education of parents and teachers, a revision of studies and play activities and an improvement in the dietary habits and nutritional status of the children.

BERKLEY, Los Angeles.

TREATMENT OF MINOR FOOT DISABILITIES. T. McW. MILLER, Edinburgh M. J. **45**:540 (Aug.) 1938.

This article belongs to the series of "Clinical Recollections and Reflections" appearing in this journal.

The author discusses the anatomy and physiology of the foot and the factors in the causation of foot disabilities and structural defects. He believes that flatfoot is diagnosed too frequently, and he sticks strictly to a definition in which the following changes are held to be characteristic: downward displacement of the head of the talus with abduction of the front of the foot, lengthening of the inner border and flattening of the longitudinal arch.

True flatfoot is classified as congenital, infantile, adolescent, infective and adult. As a congenital malformation it is rare. In infants it develops especially when there has been rickets and when there is a congenitally short tendo achillis. This can be demonstrated by the failure to dorsiflex farther than a right angle when the knee is kept straight. In such a condition the child cannot put his foot flat on the ground without abduction and eversion, which, if lasting, will produce a true flatfoot.

NEFF, Kansas City, Mo.

THEORIES OF SHOCK AND THEIR RELATION TO BURNS. J. B. DEVINE, M. J. Australia **1**:14 (Jan. 7) 1939.

Recent work on the theories of the causation of shock is reviewed. A combination of the theory that conceives of the cause as a humoral factor with that which holds that it is a nervous factor is suggested. The application of these theories to the causation of shock in burns and to the treatment of burns is described.

GONCE, Madison, Wis.

Miscellaneous

TRANSACTIONS OF THE CUBAN SOCIETY OF PEDIATRICS. Arch. de med. inf. **8**:83 (April-June) 1939.

At the 1939 meeting held in January the following subjects were discussed: hypothyroidism, tuberculosis, pertussis, abdominal conditions (appendicitis), avitaminosis B, encephalitis and malaria. A session was held for practical applications.

SANFORD, Chicago.

CONTINUOUS INTRAVENOUS DRIP INFUSION. R. STAHL and M. W. WEISBACH, München. med. Wchnschr. **86**:610 (April 21) 1939.

Stahl states that the continuous intravenous drip infusion is used extensively in the surgical and gynecologic clinics but infrequently in the medical clinics. The reason is that the surgical technic as first described required the insertion of a glass cannula into the vein. The authors decided that this was not necessary. Moreover, they felt that the narrower the lumen through which the fluid enters the vein the less chance there would be for thrombosis. The fluid would flow

more rapidly through a narrow lumen and prevent back flow of the blood. The authors describe a nonsurgical method using a no. 2 to 4 record syringe cannula. If this is similar to the needles used in this country, the method described is similar to that in general use here.

BRAHDY, Mount Vernon, N. Y.

CONTINUOUS INTRAVENOUS DRIP INFUSION. R. STAHL and H. ZEDLER, München. med. Wchnschr. **86**:613 (April 21) 1939.

The authors emphasize the importance of the intravenous drip for medical conditions. They discuss the indications and contraindications for its use in a lengthy article.

BRAHDY, Mount Vernon, N. Y.

TREATMENT BY ALTITUDE IN PEDIATRICS. P. NICULESCU and C. BARBILIAN, Med. inf. **1**:145 (March-April) 1939.

The excessive use which is generally made of heliotherapy in treating children determined Niculescu and Barbilian to insist on the superiority of the treatment by altitude. The excitement caused by the sea in addition to the excessive heliotherapy can aggravate latent tuberculosis, whereas the altitude treatment can cure even the patient with active pulmonary tuberculosis if the general condition is good. The altitude treatment can be applied during the winter, while the sea is accessible only during two and one-half months of the year, during the summer. The authors insist on the necessity of erecting permanent preventoria in protected places in the mountains in order to realize the possibility of this method of treatment in children during the winter months.

FROM AUTHORS' SUMMARY.

MISCELLANEOUS COMMUNICATIONS AT THE FOURTH INTERNATIONAL PEDIATRIC CONGRESS, ROME, SEPTEMBER 1937. Acta pædiat. **22**:400, 1938.

The results of recent research bearing on many pediatric problems are presented in abstract. The number and variety of the titles makes it impracticable to summarize or list them.

McCUNE, New York.

Society Transactions

CHICAGO PEDIATRIC SOCIETY

GERHARD KROST, M.D., *President*

Regular Meeting, Nov. 21, 1939

Value of Roentgenography in Diagnosis of Congenital Pyloric Stenosis.
DR. JOSEPH K. CALVIN and DR. EDWARD J. DENENHOLZ.

A review of the literature of congenital pyloric stenosis reveals many conflicting opinions regarding (1) the frequency with which the pyloric tumor can be palpated and the extent to which failure to feel the tumor weighs against the diagnosis, and (2) the value of roentgenography in the diagnosis of pyloric stenosis.

The cases of 128 patients with suspected congenital pyloric stenosis who were admitted to the Sarah Morris Children's Hospital (Michael Reese Hospital) from Jan. 1, 1930 to Jan. 1, 1939 are analyzed as the basis of this report. These did not include infants who entered the hospital as having suspected pyloric stenosis but who responded readily to medical treatment and who were not subjected to roentgenographic examination or operation.

Besides the 96 patients who were subsequently proved to have pyloric stenosis at operation, a pyloric tumor was thought to be palpated abdominally before operation in 3 additional patients. Two of these were operated on, no roentgenograms having been made prior to operation. No tumor was found at operation in either case. In the other case, roentgenograms showed no retention of barium, and the vomiting stopped within a few days, no operation being performed.

A diagnosis of congenital pyloric stenosis was made in 56 instances by means of the roentgenogram. In 55 cases a definite pyloric tumor was present, as shown at operation. A pyloric tumor was palpated preoperatively in 13 of these cases, or 23.6 per cent.

A diagnosis of pyloric spasm was made in 21 instances by means of the roentgenogram. The patients were not operated on and recovered under medical management within a few weeks. A tumor was thought to be palpated in 1 of the cases.

In 50 cases clinical diagnosis alone was relied on. In 41, or 82 per cent, of these there was a definite pyloric tumor, as demonstrated by operation. In 9, or 18 per cent, either no tumor or a questionable, indefinite tumor was found at operation.

Our studies indicate that the roentgenogram is a simple means of establishing an accurate diagnosis of congenital pyloric stenosis and thus differentiating it from pyloric spasm. A review of the literature demonstrates, however, that this method is not being utilized sufficiently, often being ignored, dismissed as being useless or relegated to an insignificant diagnostic position. This literature would indicate that the differential diagnosis between the two conditions still rests on clinical judgment alone, a factor which varies with every clinician and with every clinic. As operation has increasingly become the treatment of choice for pyloric stenosis, early and accurate diagnosis assumes increasing importance. Roentgenography greatly facilitates early diagnosis, at the time when the infant is in the best condition to withstand operation and before the palpation of a marked tumor is usually evident. We concede that it is at times possible to palpate the tumor in the pylorus, yet this is a personal equation, in which one or two physicians out of every ten may be able conscientiously to say that the mass is or is not palpable. Even in those cases in which a definite tumor is palpated and severe symptoms are present, the roentgenogram offers corroborative, reassuring

evidence. The roentgenogram, moreover, offers an objective standardized means of diagnosis, which appears identical whether viewed by the physician who sees only an occasional infant with suspected pyloric stenosis or by the attending physician at a large children's hospital.

DISCUSSION

DR. JOSEPH K. CALVIN: In reviewing the literature regarding the differential diagnosis between congenital pyloric stenosis and pyloric spasm and in discussing the subject with numerous pediatricians, especially as to which patients should be operated on, three main factors are considered. They are: (1) palpation or not of a tumor; (2) response or lack of response to adequate antispasmodics, and (3) roentgenographic examination after a barium sulfate meal. I believe all physicians agree that these three measures may be used to distinguish the relative degrees of stenosis or/and spasm. It is their relative value that they disagree about.

From our experience and investigation we place the roentgenogram first, because (1) it is absolutely reliable as proved at operation; (2) it is something tangible; the degree of stenosis and retention can be seen; every one can see the film; there is no personal question; (3) it has been a harmless procedure in our series of cases. Palpation of the tumor mass we place second, because it is difficult or impossible in many cases to feel the tumor, as it may be behind the air-containing or food-containing antrum or up under the liver, and because palpation requires time and considerable experience involving a large personal equation. Response to therapy we consider third in importance, because it is not altogether reliable. Occasional patients with stenosis who continue to have 50 to 60 per cent retention in the stomach after four hours for months under adequate antispasmodic therapy may apparently clinically improve, gain weight moderately and vomit only occasionally, whereas infants with severe pyloric spasm with no retention may continue to vomit at least for some weeks on this same regimen.

We have 3 typical cases of pyloric stenosis with roentgenograms taken after barium meals. In the first case there was 50 to 60 per cent retention in a male infant aged 6 weeks with pyloric stenosis and a palpable pyloric tumor. Serial plates over a period of six weeks still show 50 per cent retention, even though the infant is receiving adequate antispasmodics and is gaining fairly well and not vomiting. The tumor can still be felt. Here, in spite of clinical improvement, considerable retention is still present. Should this infant be operated on?

In the second case there was 60 per cent retention in an infant aged 9 weeks; no tumor was palpable. Serial plates over a period of two months still show a 50 per cent retention in spite of adequate antispasmodics. The infant is gaining fairly well and vomiting only occasionally. Roentgenographic evidence of retention of barium is the only conclusive finding here, as no tumor was palpable and there is a fairly good response to medical therapy. These 2 cases are borderline cases in regard to operation, for although there is fair clinical improvement there is still plenty of retention, which probably means that the stomach has dilated and hypertrophied enough to compensate for the partial obstruction, forcing enough food through to indicate a satisfactory clinical improvement.

The third case is that of a child aged 3 years who had several periods of explosive vomiting during infancy. Recently he again began projectile vomiting, and roentgenograms showed 80 per cent retention and an elongated pyloric canal (pathognomonic for congenital pyloric stenosis). Operation revealed a typical pyloric stenosis, apparently congenital, with a markedly dilated and hypertrophied stomach. This raises the interesting question of how many infants with pyloric stenosis of moderate degree who respond fairly well to medical treatment really have obstructive difficulties in later childhood or adult life.

DR. JOSEPH BRENNEMANN: No matter how much is known about pyloric stenosis and how much of it one has seen, there is still something mysterious about it. I think a paper is always interesting that advocates a procedure that

one has never tried. So far as I can recall, my associates and I have never given a child a barium sulfate meal to see whether he had a pyloric stenosis. We feel that we can tell pretty well without that, and after all this is an extra procedure to which the child is submitted, and I am not yet entirely convinced that it is necessary or does any good. Our own procedure is something like this: The child is suspected of having pyloric stenosis. Depending on the age and condition of the child and the decisiveness of the symptoms, we feel that we can often tell whether we have to deal with a true stenosis or a spasm. Whether they are etiologically the same is beside the question. To us they present two different clinical pictures. The child is offered a bottle of sugar water while the examiner sits at the patient's left with his warm hand laid flat on the child's abdomen and the middle finger of the left hand bent into the space outlined by the costal border and the right border of the right rectus muscle. He watches the peristaltic waves and keeps feeling. He may or may not feel the tumor at this time if it is present, but he almost invariably can just after the child has vomited projectilely. I am sure that we can feel the tumor if it is present in well over 90 per cent of cases, and we never like to have a child operated on until we can feel a tumor. Even though we feel a tumor we give the child the benefit of the doubt for twenty-four hours by the use of atropine or possibly phenobarbital, and we have a fondness for condensed milk, which does not coagulate in the stomach. If the child still vomits almost everything and we feel a definite tumor, we submit him to operation. Tumor or no tumor, we feel there is ultimately only one criterion for determining the need of an operation, and that is whether the baby gets along all right.

I am a little confused about Dr. Calvin's designation of those cases in which the patient gets along well or moderately well in spite of the fact that according to the roentgenogram he has a true hypertrophic pyloric stenosis. We would call the condition in those cases spasm of the pylorus and would expect the patients to get along all right.

DR. L. W. SAUER: Dr. Denenholz' paper is very interesting. The amount of fecal matter and the weight curve are most valuable aids in determining the degree of pyloric potency or obstruction. We always try small feedings of thick cereal (not over 2 ounces [60 cc.] seven times a day), phenobarbital and 2 ounces (60 cc.) retention enemas of tepid water several times a day. The infant is kept in the crib on the right side with the head elevated. If the weight continues to decrease rapidly or if it remains stationary for two weeks, and if the amount of fecal matter fails to increase after thick cereal feedings have been faithfully tried, surgical intervention is indicated. To wait too long increases the surgical risk and prolongs the suspense. We have not used the roentgenogram in diagnosis or differential diagnosis in the last fifteen years. Not more than a third of our patients required operation.

DR. JULIUS H. HESS: I think I have experienced a great deal of satisfaction in the use of the roentgenogram in diagnosis. I have not the skilful fingers that Dr. Brennemann has, and in many cases in which there was a doubt as to the diagnosis, I think it has been proved, to my satisfaction at least, that the patient had stenosis with abnormal gastric retention. I think the roentgenogram has played another role. A considerable number of patients with pylorospasm to whom I have given a barium sulfate meal stopped vomiting within a few days. I believe it to have been of value both in differential diagnosis when there was doubt as to the presence of organic obstruction and also in determining the degree of obstruction in the presence of true hypertrophic pyloric stenosis.

DR. E. J. DENENHOLZ: I want to thank Dr. Brennemann for not "picking on" us more than he did, because I know how he feels on this particular subject. We should like to emphasize, however, that for the average clinician the roentgenogram can be a definite aid in the diagnosis. We realize, of course, that we are going to get a good deal more controversy than came forth tonight, because we know from a review of the literature that this particular use of the roentgenogram is condemned by many.

With respect to Dr. Sauer's discussion, we reviewed our cases and were unable to distinguish the cases of severe spasm from those of organic stenosis by observation of the stools and the weight. Some patients with marked loss of weight and constipation had no tumor. It was also of interest to note that the length of time the baby vomited had no relation to whether or not a tumor was found. Thus, there were some who had a history of vomiting for two weeks in whom a tumor was found, and others had a history of vomiting for three or four weeks, and no tumor was found.

We purposely avoided any discussion on whether pylorospasm and pyloric stenosis are two separate entities or whether they are different phases of the same underlying disorder, because we feel that we can offer nothing of value in this regard.

We have had much the same experience as has Dr. Hess, but we did not mention it here because we did not wish to appear to offer this method as a panacea. However, we observed in 8 cases in our series that a few days after the roentgenogram was made the vomiting stopped, the peristaltic waves disappeared and the patient gained weight.

Periarteritis Nodosa Complicating Scarlet Fever, with an Unusual Syndrome of Nephritis and Polyneuritis. DR. A. L. HOYNE and DR. MATTHEW M. STEINER.

This paper will be published in full, with discussion, in a later issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN.

Modern (Aseptic) Nursery Technic (Moving Picture). DR. L. D. MINSK and MR. J. J. MCDONALD.

Observation at the Cradle, in Evanston, Ill., during the past ten years seems to show that hand-borne infections can be eliminated by the application of the so-called Dick aseptic nursery technic. The purpose of the new Cradle building is to find out the best way to control also the air-borne infections. For this purpose three separate units in the Cradle were constructed. Each unit is designed to test the efficiency of one modern method of preventing air-borne infections, each method being based on a different principle.

The three principles are (1) air conditioning, (2) light barriers and (3) mechanical barriers.

The three units differ only in these three basic principles, all other features being identical (size, equipment, nursing staff, number of infants and so forth).

The first unit consists of twelve separate cubicles, open at the front. Each cubicle is individually air conditioned with 100 per cent outside air and has an approximate air content of 108 cubic feet (3 cubic meters). Fresh, conditioned air with a temperature of 75 F. and a relative humidity of 40 per cent enters near the ceiling of each cubicle at the rate of approximately 78 cubic feet per minute; the air leaves near the floor of each cubicle at a rate of 59 cubic feet (1.7 cubic meters) per minute, going out to the roof. There is a complete change of air about every three minutes. Thermostats are so placed as to maintain a constant temperature throughout the unit. Thus the only principle applied in this first unit to prevent air-borne infections is that of air conditioning.

The second unit also contains twelve cubicles, provided with air conditioning, as the first unit, but in addition to this is equipped with bactericidal lights. Prof. William F. Wells, of the University of Pennsylvania, who has made many important contributions to the development of light as a bactericidal agent, devised this unit. The spectrum band of this light differs from that of the customary ultraviolet radiation in that approximately 90 per cent of its rays are 2,537 angstrom units. In this unit there are six cubicles separated by solid partitions and provided with a curtain of light only at the front; the remaining six cubicles also have a light curtain at the front, but instead of a partition these have a light barrier between each two cubicles. The curtains of light are so designed that

only a harmless fraction of the emanation of light reaches the corner of the cubicle where the head of the child is exposed. The nurses' eyes are not brought into the range of the overhead lights. The nurses are further protected by head shields. The rays kill the bacteria passing through the light barrier. Wells has demonstrated that the light is especially effective against the type of infection produced by the evaporation of droplets coughed and sneezed into the atmosphere. Ventilation tests on the bacterial tightness of the light curtains indicated that from 98.9 to 99.7 per cent of the test organisms were killed as they passed through the wall of light.

The third unit also contains twelve cubicles provided with air conditioning, but, in addition to that, it has a special type of mechanical barrier devised by Prof. James Reyniers of the University of Notre Dame. Dr. Reynier's basic principle is to protect the infants from cross infections by mechanical barriers. The representative cubicle of this unit is closed and consists of two distinct sections, separated from each other by a glass partition, an inner section for the infant and an outer section for the nurses. The latter contains the cubicle supplies. Each section has its own air intake and exhaust. The nurse enters the outer section of the cubicle, makes preparations for the care of the infant, raises the glass window in the partition to her shoulder level, attends the infant and then closes the window. The air supply of the two sections of the cubicle is so arranged that the air pressure maintained in the infant's section is much greater than that in the nurse's section; thus, when the window is raised air from the nurse's section does not enter the infant's section.

Clinical observations supplemented by laboratory tests should ultimately decide which of the three principles is most successful in preventing the spread of airborne infections in a nursery.

DISCUSSION

DR. PHILIP ROSENBLUM: What is the milk preparation that is autoclaved?

DR. JULIUS HESS: I wonder if he could give us the results on the incidence of infections since this plan of operation was started.

DR. ARCHIBALD HOYNE: I should like to inquire what the difference is between nursing technic, so-called, in the Cradle since 1929 and the medical aseptic technic as developed by Chapin and Richardson in Providence in 1912. After seeing these attractive pictures one wonders how far such precautions are going to go. The equipment in the Cradle is marvelous. On the other hand, it seems that one can get along fairly well without such expensive equipment. Last year at Municipal Contagious Diseases Hospital a daily average of 100 infants less than a year old were treated for whooping cough. Some had pneumonia and other complications, but there were no cross infections. The plan of technic used in this hospital is modeled after that of Chapin in Rhode Island.

DR. MAURICE L. BLATT: Dr. Minsk and the Cradle are to be most highly complimented not only for the pictures they have presented but for the achievements shown in these pictures. They have demonstrated better than has been demonstrated previously the practical utilization of the knowledge of methods of prevention of cross infections. Although such methods, because of their cost, are not practical in most institutions, they constitute a highly commendable research in the method of control of infection in this group of very susceptible infants.

DR. JOSEPH BRENNEMANN: This is, of course, a tremendously interesting demonstration. I should like to know what kind of mask the nurses use and whether there is any trouble in teaching them to use the mask so as to achieve bacteriologic safety.

I recently went to a place where there were many premature infants. The nurse in charge, who has been there for a long time, said they did not formerly use masks and she was sure they did not have more cross infection than they do now. At another institution, where I saw a newborn baby, I put on a cap and gown, washed my hands and behaved very properly bacteriologically. The

nurse was equipped similarly, but when she wanted to talk to me she placed her hands directly over her mouth, pulled the mask down, talked to me for some time, put it back again and then went on to take care of the infant without washing her hands.

I think the last word has not been said about masks. I think that in the hands of those who are not bacteriologically trained and bacteriologically conscious they may do more harm than good in isolated instances.

The infants that Dr. Chapin put out into foster homes, as I understand it, were infants that would ordinarily be found in infant wards and not in adoption centers. There is a difference. I think it is fairly well recognized that in the first three months of life infants are relatively immune to infection rather than predisposed to it. After the third month they begin to eat things. It is certainly rare to see epidemics of infections of the respiratory tract in maternity wards. The frightful diarrheal infections that have been seen in recent times are something new.

DR. L. D. MINSK: Dr. Rosenblum asked about the autoclaving of milk. For a long time we have autoclaved whole milk and evaporated milk mixtures. We now autoclave breast milk, and more recently we began to do the same to protein milk and found that it can be done safely without curdling.

Orange juice is not autoclaved. You saw how it is prepared: the oranges are washed with alcohol and sterilized in hot water and cut with a sterile knife. The juice is fed within half an hour after extraction.

In reply to Dr. Hess, it is too early to give results. We have had several infants come in with infections of the upper part of the respiratory tract, and there has been no transmission of the infection to another infant in the same unit since we moved into the new, air-conditioned building. In one unit at different times there were four nurses with colds, and none of the infants contracted a cold.

In previous years there were two seasons—the autumn months of October and November and the late winter and early spring—when we would have a small epidemic of infections of the respiratory tract. If an infant with the infection was admitted to a unit there would practically always be a spread to other babies in that unit. Dr. Sauer reported such an epidemic, which occurred among 10 babies in the summer. Since the new building has been in use there has been no such epidemic.

Some of the members remember the work of Dr. Chapin of New York. The mortality among infants in his institution was so high that he boarded the infants in foster homes to reduce the mortality. Children are not so susceptible as infants to diarrheal infections and infections of the respiratory tract.

Dr. Blatt said that this method is not practical. I think a good deal of it is. Some of the measures instituted about two years ago by the department of health show that they are practical, especially such things as an attendant's scrubbing the hands well before going to another infant, which, after all, is the most important procedure. That can be carried out in any institution.

I expected Dr. Brennemann to mention masks. Those in use are made of two layers of gauze between which is a layer of thick cotton material which acts as a filter. In the upper margin is a pliable metal strip which is molded and fitted snugly over the nose and cheeks. The air does not go out of the margins of the mask—my glasses do not fog when wearing this mask—it is really a filter. We have made no bacteriologic tests with these masks. The nurses are instructed in the use of the masks. All must scrub their hands if a mask is touched when in use. They do not remove the masks while in the unit. No one enters a unit without a mask.

In reply to the other remark of Dr. Brennemann, it is true that infants in the home do not contract infections of the upper part of the respiratory tract easily. The infants in the Cradle stay on the average of six to eight weeks. We always had epidemics of infections of the respiratory tract in the old buildings, but they were not serious except on rare occasions. Nurses are always taken off duty when they are known to have colds.

Book Reviews

Medical Climatology: Climatic and Weather Influences in Health and Disease. By Clarence A. Mills, Ph.D., M.D. Price, $4.50. Pp. 296, with 90 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1939.

The author presents the results of an extensive analysis of the effects of climate on mankind in relation to growth, fertility, disturbances of metabolism, infectious diseases, degenerative diseases, dental caries and mental function. His observations reveal that residents of storm areas, in which sudden changes of temperature and barometric pressure are frequent, are most susceptible to infections of the respiratory tract, appendicitis and diseases of metabolism. A mass of statistical data with reference to death rates is presented to support his observations. The book is also well illustrated with charts of storm areas throughout the world.

The reviewer received the impression that too much weight is given to the effect of climate in the incidence of certain types of illness and that factors such as race and occupation are not adequately considered. In the case of tuberculosis, evidence is presented that persons who become infected during the winter months have in general a shorter life expectancy than those in whom the disease appears during the summer months. Although we know that tuberculosis frequently is diagnosed for the first time following a severe infection of the respiratory tract during the winter months, it is not always possible to determine when the disease began. Furthermore, early recognition and proper treatment of persons with tuberculosis which appeared during the winter months have brought results just as favorable as those obtained when the illness was diagnosed during the summer months.

The author stresses the importance of "climatic driving force and weather instability" in diseases of metabolism and the degenerative diseases. He feels that residents of the temperate zone, Americans particularly, are living at too fast a pace and thereby deplete their physical resistance, a consequence which is followed by functional breakdown, manifested in diseases of metabolism and degeneration. He believes that they would live longer if they were subjected to less stress in living. Areas in the United States are mentioned which are relatively storm free, have mild fluctuations in temperature and exhibit proper relative humidity throughout the year, and these locations are recommended for patients with most chronic and degenerative illnesses.

The book is clearly and forcefully written and is interesting reading. Physicians and public health workers will find it of considerable value in explaining the seasonal incidence of selected diseases. However, much work is yet to be done in this field to obtain reliable information on the relation of climate and diseases now incompletely understood.

Spätschicksale atrophischer Säuglinge: Zur Frage der Entstehung exogener Schwachsinnszustande. By H. Lange-Cosack. Price, 5.50 marks. Pp. 69. Leipzig: Georg Thieme, 1939.

The study reported in this book was based on 88 cases in which the patients had had severe infantile atrophy for at least two and a half or three months. Seventy-seven of these patients could be reexamined, most of them at the age of 12 to 14 years, and in 11 instances reports were obtained. The development of these patients was compared, when possible, with that of their siblings, and the mentality of their parents and of other members of their families was considered. The incidence of feeblemindedness in the population at large was also taken into consideration. Cases of severe atrophy involving infants who were seriously retarded were excluded.

The incidence of feeblemindedness was 17, or 19.3 per hundred, exceeding that of the population at large. However, within the families of the patients the incidence of feeblemindedness was also rather high, although such an *Anlage* could not account entirely for the high incidence among the patients proper. The conclusion is reached that severe pedatrophy, starting within the first months of life and extending over a prolonged period of time, is not always without detrimental influence on the further cerebral development of the child.

The author is rather cautious in his statements. Perusal of this little monograph demonstrates the difficulties which beset such an inquiry, making it well nigh impossible to arrive at any definite proof for the present. For this reason, a more detailed discussion of the work is omitted.

Congenital Malformations: A Study of Parental Characteristics with Special Reference to the Reproductive Process. By Douglas P. Murphy, M.D. Price, $1.50. Pp. 98, with 55 tables, 7 graphs and 1 photograph. Philadelphia: University of Pennsylvania Press, 1939.

This book is the report of a study of 1,476 malformed infants in 890 families for a period covering five years. The results are presented by means of tables and are of great interest. Some high points are that gross congenital malformations afflict 1 in 213 children born alive and that about 25 per cent of congenitally malformed persons are stillborn. The study revealed a probability twenty-five times greater than normal that parents who already have 1 malformed child will bear another, but it showed no relation to social status, chronic illness, syphilis, season of the year, occupation of the parents, contraceptive methods or pelvic irradiation during pregnancy. The diets of the mothers of the defective children were found to be significantly lacking in calcium, phosphorus, iron and vitamins B, C and D. Many other results of the study are intensely interesting and should be read in full by any one concerned with these conditions.

A Handbook of Elementary Psychobiology and Psychiatry. By Edward G. Billings, M.D. Price, $2. Pp. 271, with 12 illustrations. New York: The Macmillan Company, 1939.

This handbook of psychiatry was written for medical students and general practitioners of medicine. It presents the psychobiologic description of behavior as developed by Dr. Adolph Meyer and interpreted by the author.

There is an excellent dissertation on the psychobiologic point of view, followed by a detailed description of procedures for psychiatric examinations. Chapters are devoted to the common mental disorders—psychoneuroses, psychoses, drug addiction, alcoholism, poisons, etc. With the description of the disorders, there are suggestions on methods of management of the patients and details of psychotherapy.

The book is well written, interesting and valuable as a text. From the standpoint of the pediatrician or the general practitioner it is unfortunate that there are still schools of psychiatry, each having its own confusing nomenclature. The terminology in places detracts from an otherwise lucid book.

Attaining Womanhood: A Doctor Talks to Girls About Sex.—By George W. Corner, M.D. Price, $1. Pp. 95, with 15 illustrations. New York: Harper & Brothers, 1939.

This small volume is a counterpart of a previous publication (Attaining Manhood: A Doctor Talks to Boys About Sex, New York, Harper & Brothers, 1938) by the same author, who is professor of anatomy at the University of Rochester School of Medicine and Dentistry. In a similar manner this companion volume adapts the available knowledge regarding sexual development and reproduction for intelligent comprehension by the adolescent girl. The simplicity of the terms and the skill with which biologic analogy has been utilized in demonstrating the physiology of menstruation and reproduction, in addition to

the anatomic illustrations, enhance the value of the publication not only to the child but to the parent, the educator and the physician. The discussion of sex attraction and sex conduct has served as an excellent basis for rational consideration of the various sex problems which may be encountered. A brief discussion of venereal disease in conformity with the present educational program along these lines is included.

Fractures. By Paul B. Magnuson, M.D., F.A.C.S. Third edition. Price, $5. Pp. 511, with 317 illustrations. Philadelphia: J. B. Lippincott Company, 1939.

This is an excellent textbook for practitioners who are treating the majority of fractures which occur in everyday life. The text is clearly and simply written, and there is no great amount of unnecessary detail.

Every common type of fracture is discussed and illustrated either by roentgenograms or by diagrams with the exception of fractures of the jaw, which the author feels should be relegated to a special field. There is a brief but comprehensive introduction into the principles of handling cases of fracture. There are numerous innovations and improvements over standard methods for treating some of the commonest injuries, and the mechanical principles set forth are sound. The chapter on hip fractures is thorough, yet not too detailed to be understandable. There is an excellent chapter on fractures of the skull as well as one on fractures of the spine.

Simplicity and moderate conservatism are the two keynotes found throughout the book. The author does not hesitate to advise certain operative procedures, but he recommends them with caution. There is no special chapter devoted to fractures peculiar to children. There is an interesting and practical section on physical therapy and on the after-care of injuries. The author has given a four page reference table listing the various bones, the position for maintenance of reduction, the type of splinting, the length of time required for healing and the time to begin physical therapy. A most excellent bibliography is included.

Brucellosis in Man and Animals. By I. Forest Huddleson, D.V.M., M.S., Ph.D. Contributing Authors: A. V. Hardy, M.S., M.D., Dr.P.H.; J. E. Debono, M.D., M.R.C.P., and Ward Giltner, D.V.M., M.S., Dr.P.H. Price, $3.50. Pp. 339, with 40 illustrations. New York: Commonwealth Fund, Division of Publications, 1939.

This is the second book on brucellosis that Dr. Huddleson has written. The first, published five years ago, was a treatise on methods of laboratory diagnosis. The present publication not only brings that phase of the subject up to date but adds a wealth of clinical material. Dr. J. E. Debono describes the caprine form of the disease as he has studied it in the Island of Malta; Dr. A. V. Hardy contributes the results of his survey of brucellosis in the United States, and Dr. Ward Giltner discusses the animal and human health problems relating to the disease.

As brucellosis is probably more widespread than has been thought, such a book, which familiarizes one with the protein manifestations of the disease and the available methods of establishing a diagnosis, should prove of definite value to the medical profession.

Alteraciones vertebrales en el tetanos. By José Bonaba and Luis Arturo Pieroni. Price not given. Pp. 49, with 23 illustrations. Montevideo: Imprenta "Rosgal," de Hilario Rosillo, 1939.

From a study of 9 personal cases and of 41 cases from the literature the authors conclude that in many cases of tetanus there are changes in the spinal column (dorsal kyphosis, scoliosis or forward projection of the sternum). These can be found by means of the roentgenogram and occasionally by inspection. Such changes, they report, existed in from 20 to 100 per cent of the cases studied (in their own series, in 60 per cent). The greatest frequency is that in boys

from 10 to 15 years of age. The authors believe that the condition is the result of intense muscular traction that produces trabecular fracture at the point of greatest strain. The process is benign and self limiting.

The plates in the book are well chosen, and the authors' arguments are interesting and convincing.

Synopsis of Pediatrics. Third edition. By John Zahorsky, M.D., assisted by T. S. Zahorsky, M.D. Price, $4. Pp. 430, with 144 illustrations and 9 color plates. St. Louis: C. V. Mosby Company, 1939.

This small book is well fitted for the purposes which it is to serve, namely, to convey the main points of pediatrics to medical students and general practitioners and to afford a basis for lectures to medical students. It is well illustrated and well got up. Some of the colored illustrations are excellent. In order to condense the material into a small number of pages, it has been necessary to use a fine type which is rather hard to read. On the whole the book is to be recommended for the purposes mentioned.

Alimentacão do lactente sadio. By Cesar Beltrão Pernetta. No price given. Pp. 122, with 15 tables. São Paulo, Brazil: Empresa grafica da revista dos tribunais, 1939.

This is a short book on infant feeding, written in Spanish. It is good to find that the author takes up nearly half of the book with the advantages and technic of breast feeding. This section is illustrated with tables and drawings. A brief but complete résumé is then given of the various forms of artificial foods (cow's milk formulas preferred), mixed feeding and medicinal foods that may be used. The book is interesting and well prepared.

News and Comment

GENERAL NEWS

American Board of Pediatrics.—An examination will be held by the American Board of Pediatrics on Nov. 17, 1940, in Memphis, Tenn., preceding the annual meeting of the American Academy of Pediatrics. All schedules for the spring examinations are now filled.

DEATHS

Prof. Sebastiano Cannata, director of the pediatric clinic of the Royal University of Palermo, died on December 17, at the age of 60 years.

Directory of Pediatric Societies*

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Prof. Luigi Spolverini, Policlinico Lungo Tevere Melini 24, Rome, Italy.
Secretary: Professor Vitetti, Rome, Italy.
The meeting is postponed to an indefinite date.

American Committee:
Chairman: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
General Secretary: Dr. Kenneth D. Blackfan, 300 Longwood Ave., Boston.
Assistant Secretary-Treasurer: Dr. Charles F. McKhann, 300 Longwood Ave., Boston.

Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St. W., Montreal.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

British Paediatric Association

President: Prof. Charles McNeil, 44 Heriot Row, Edinburgh, Scotland.
Secretary: Dr. Arthur G. Maitland Jones, 31A Weymouth St., London, W. 1.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

Royal Society of Medicine, Section for the Study of Disease in Children

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

President: Prof. S. Rosenbaum, 26 Bialikstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

SOCIEDAD CUBANA DE PEDIATRÍA

President: Dr. Clemente Inclan Costa, Manrique 48, Habana.
Secretary: Dr. Serafin Falcon Lopez, Calle B No. 356, Vedado, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Jorge Muñoz Turnbull, Av. Alvaro Obregón 186, Mexico, D. F.
Secretary: Dr. Fernando López Clares, Medellín 191, Mexico, D. F.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincaré, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue du Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Albert D. Kaiser, 16 N. Goodman St., Rochester, N. Y.
Secretary: Dr. Hugh L. Dwyer, 315 Alameda Rd., Kansas City, Mo.
Place: New York. Time: June 10-14, 1940.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. J. B. Bilderback, 1020 S. W. Taylor St., Portland, Ore.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Hotel Peabody, Memphis, Tenn. Time: Nov. 18-20, 1940.
Region I. Place: Mayflower Hotel, Washington, D. C. Time: April 4-6, 1940.
Region II. Place: Edgewater Gulf Hotel, Edgewater Park, Miss. Time: March 15-16, 1940.
Region IV. Place: Seattle, Wash. Time: May 30-June 1, 1940.

AMERICAN HOSPITAL ASSOCIATION, CHILDREN'S HOSPITAL SECTION

Chairman: Miss Mabel Binner, Children's Memorial Hospital, Chicago.
Secretary: Winifred Culbertson, Children's Convalescent Hospital, Cincinnati.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Herbert B. Wilcox, 39 E. 75th St., New York.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis.
Place: Skytop, Pa. Time: May 2-4, 1940.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. L. M. Lindsay, 815 Medical Arts Bldg., Montreal.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.

Society for Pediatric Research

President: Dr. Daniel C. Darrow, 330 Cedar St., New Haven, Conn.
Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia.
Place: Skytop Lodge, Skytop, Pa. Time: Afternoon of May 1 and morning of May 2, 1940.

SECTIONAL

Intermountain Pediatric Society

President: Dr. Eugene Smith, 385–24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

New England Pediatric Society

President: Dr. R. Cannon Eley, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. James Marvin Baty, 319 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

North Pacific Pediatric Society

President: Dr. Frederick Fischer, 407 Riverside Ave., Spokane, Wash.
Secretary: Dr. C. L. Lyons, Paulsen Medical-Dental Bldg., Spokane, Wash.

Rocky Mountain Pediatric Society

President: Dr. John Schoonover, Republic Bldg., Denver.
Secretary: Dr. F. Craig Johnson, 1850 Gilpin St., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 7:30 p. m.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. Hughes Kennedy Jr., Highland Plaza Apts., Birmingham, Ala.
Secretary: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables, Fla.

STATE

Alabama Pediatric Society

President: Dr. Stewart H. Welch, 1117 S. 20th St., Birmingham.
Secretary-Treasurer: Dr. William R. Britton, 4 Catoma St., Montgomery.

Arkansas State Pediatric Association

Chairman: Dr. G. D. Murphy, 112 Peach St., El Dorado.
Secretary: Dr. Madeline M. Melson, 909 Main St., Little Rock.

California State Medical Society, Section on Pediatrics

Chairman: Dr. Harold K. Faber, 2341 Clay St., San Francisco.
Secretary: Dr. Hartzel H. Ray, 23–2d Ave., San Mateo.

Florida State Pediatric Society

President: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables.
Secretary: Dr. George N. Leonard, 605 Lincoln Rd., Miami Beach.
Place: Concurrent with state association meeting at time of convention.

Georgia Pediatric Society

President: Dr. L. H. Muse, 384 Peachtree St. N. E., Atlanta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Business Meeting. Place: Savannah. Time: April 1940.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. Oliver L. Stringfield, 1416 Bedford St., Stamford.
Secretary: Dr. Joseph L. Hetzel, 103 N. Main St., Waterbury.
Time: Three meetings a year.

Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. H. William Elghammer, 5307 Hyde Park Blvd., Chicago.
Secretary: Dr. Bert I. Beverly, 8 S. Michigan Ave., Chicago.
Place: Peoria. Time: May 22, 1940.

Indiana State Pediatric Society

President: Dr. O. N. Torian, 23 E. Ohio St., Indianapolis.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Morgan J. Foster, 837 Higley Bldg., Cedar Rapids.
Secretary-Treasurer: Dr. Arnold M. Smythe, 406–6th Ave., Des Moines.

Louisiana State Pediatric Society

President: Dr. Phillip C. De Verges, Audubon Bldg., New Orleans.
Secretary-Treasurer: Dr. W. C. Rivenbark, 220 Physicians and Surgeons Bldg., New Orleans.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Paul W. Beaven, 26 S. Goodman St., Rochester.
Secretary: Dr. Leslie O. Ashton, 850 Park Ave., New York.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. John M. Higgins, 600 S. Wilbur Ave., Sayre.
Secretary: Dr. John D. Sturgeon Jr., 22 N. Gallatin Ave., Uniontown.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. Allan L. Richardson, 3001 W. Grand Blvd., Detroit.
Secretary: Dr. Ward L. Chadwick, 524 Medical Arts Bldg., Grand Rapids.

Mississippi State Pediatric Society

President: Dr. Guy C. Jarratt, 920 Crawford St., Vicksburg.
Secretary-Treasurer: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Place: To be designated by society. Time: Yearly.

Nebraska Pediatric Society

President: Dr. Herman M. Jahr, 1120 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. Elmer W. Bantin, 440 Aquila Court Bldg., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Marion Y. Keith, 369 N. Elm St., Greensboro.
Secretary: Dr. G. W. Kutscher Jr., 176 Woodfin St., Asheville.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. A. L. Salomon, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Ben H. Nicholson, 301 W. 12th St., Oklahoma City.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. D. Lesesne Smith Jr., 187 Oakland Ave., Spartanburg.
Secretary-Treasurer: Dr. William Weston Jr., 1428 Lady St., Columbia.

TENNESSEE STATE PEDIATRIC SOCIETY

President: Dr. William E. Van Order, 546 McCallie Ave., Chattanooga.
Secretary: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.

TEXAS PEDIATRIC SOCIETY

President: Dr. T. A. Tumbleson, 2100 North St., Beaumont.
Secretary-Treasurer: Dr. F. H. Lancaster, 4409 Fannin St., Houston.
Place: Dallas. Time: May 15, 1940.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. W. Ambrose McGee, 616 W. Grace St., Richmond.
Secretary: Dr. John M. Bishop, Medical Arts Bldg., Roanoke.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. J. L. Blanton, 207 Fairmont Ave., Fairmont.
Secretary: Dr. Theresa O. Snaith, 450 Center Ave., Weston.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. N. C. Wetzel, 2103 Adelbert Rd., Cleveland.
Secretary: Dr. Fred Rittenger, 10515 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. T. B. Verner, 170 St. George St., Toronto, Canada.
Secretary: Dr. D. V. Hutton, 170 St. George St., Toronto, Canada.

BRONX PEDIATRIC SOCIETY

President: Dr. Harry S. Altman, 940 Grand Concourse, New York.
Secretary: Dr. David Zahn, 2474 Valentine Ave., New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. Benjamin Kramer, 6 Pierrepont St., Brooklyn.
Secretary: Dr. John A. Monfort, 861 Carroll St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Fourth Wednesday of each month, except May, June, July, August and September.

Central New York Pediatric Club

President: Dr. Frank van der Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Thursday of April and September.

Chicago Pediatric Society

President: Dr. Gerard N. Krost, 2376 E. 71st St., Chicago.
Secretary: Dr. George F. Munns, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

Dallas Pediatric Society

President: Dr. Edgar Loomis, 351 W. Jefferson Ave., Dallas, Texas.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmont Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

Detroit Pediatric Society

President: Dr. William O'Donnell, 1553 Woodward Ave., Detroit.
Secretary: Dr. Robert Mason, 5140–2d Blvd., Detroit.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

Fulton County Medical Society, Pediatric Section (Atlanta, Ga.)

Chairman: Dr. Stephen C. Redd, 157 Forrest Ave. N. E., Atlanta.
Secretary: Dr. C. Dixon Fowler, Medical Arts Bldg., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

Houston Pediatric Society

President: Dr. James H. Park Jr., 3717 Main St., Houston, Texas.
Secretary-Treasurer: Dr. Thomas J. Donovan, 2418 Travis St., Houston, Texas.
Place: Houston Club. Time: Third Monday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. John Aull, 1103 Grand Ave., Kansas City.
Secretary: Dr. George Herrman, 1107 Bryant Bldg., Kansas City.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. H. R. Cooder, 3875 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Paul M. Hamilton, 248 E. Main St., Alhambra, Calif.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd.
Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Benjamin Stoloff, 1149 Eastern Parkway, Brooklyn.
Secretary: Dr. Harry Apfel, 988 Park Pl., Brooklyn, N. Y.
Place: 1313 Bedford Ave., Brooklyn. Time: 9.00 p. m., second Monday of each month, October to March, inclusive.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. James Dobbins, 42-04 Ditmars Blvd., Long Island City, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. Harry H. Donnally, 1612 I St. N. W., Washington, D. C.
Secretary-Treasurer: Dr. Harry A. Spigel, 2647 Connecticut Ave. N. W. Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of October, January, February, March and April.

Memphis Pediatric Society

President: Dr. Barton Etter, 376 S. Bellevue St., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

Milwaukee Pediatric Society

President: Dr. S. F. Morgan, 5630 N. Lake Dr., Milwaukee.
Secretary-Treasurer: Dr. F. R. Janney, 1411 Wauwatosa Ave., Wauwatosa, Wis.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Rustin McIntosh, Babies Hospital, New York.
Secretary: Dr. Leslie O. Ashton, 850 Park Ave., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

Northwestern Pediatric Society

President: Dr. Roland E. Nutting, 205 W. 2d St., Duluth, Minn.
Secretary-Treasurer: Dr. John M. Adams, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Oklahoma City Pediatric Society

President: Dr. A. L. Salomon, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Time: Every month, except June, July and August.

Philadelphia Pediatric Society

President: Dr. Pascal F. Lucchesi, 4000 N. Front St., Philadelphia.
Secretary: Dr. Aims C. McGuinness, Children's Hospital, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to April, inclusive.

Pittsburgh Pediatric Society

President: Dr. E. R. McClusky, 3200–5th Ave., Pittsburgh.
Secretary-Treasurer: Dr. Carl Ruder, 646 Washington Rd., Mount Lebanon, Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate month from October to June, inclusive.

Richmond Pediatric Society

President: Dr. Emily Gardner, 1100 W. Franklin St., Richmond, Va.
Secretary-Treasurer: Dr. T. Stanley Meade, 913 Floyd Ave., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., first Thursday of each month, except July, August and September.

Rochester Pediatric Society

President: Dr. David Wolin, 16 N. Goodman St., Rochester, N. Y.
Secretary: Dr. W. L.. Bradford, 16 N. Goodman St., Rochester, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Second Friday of each month.

St. Louis Pediatric Society

President: Dr. Max Deutch, 634 N. Grand Blvd., St. Louis.
Secretary-Treasurer: Dr. Peter G. Danis, 634 N. Grand Blvd., St. Louis.
Place: St. Louis Medical Society Bldg. Time: Third Friday of ech month from September to June.

Seattle Pediatric Society

President: Dr. Jay I. Durand, 1305–4th Ave., Seattle.
Secretary: Dr. Frederick B. Joy, 1215–4th Ave., Seattle.
Place: College Club. Time: Third Friday of each month, 6:30 p. m.

Southwestern Pediatric Society

President: Dr. E. Earl Moody, 829 S. Alvarado Ave., Los Angeles.
Secretary: Dr. Norman Nixon, 1136 W. 6th St., Los Angeles.
Place: Jonathan Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Yark Osterlin, Central Michigan Children's Clinic, Traverse City, Mich.
Secretary: Dr. D. Murray Cowie, University of Michigan, Ann Arbor, Mich.
Time: Nov. 15-16, 1940.

Westchester County Medical Society, Pediatric Section (New York)

President: Dr. M. Bernard Brahdy, 531 E. Lincoln Ave., Mount Vernon.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Ave., Rye.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October December, February and April.